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The Responsibilities of The Medical Profession in the Use of X-rays and Other Ionizing Radiation

UNITED NATIONS SCIENTIFIC COMMITTEE ON THE EFFECTS OF ATOMIC RADIATION

FOREWORD

The statement which follows is the more detailed of two statements prepared by the United Nations Scientific Committee on the Effects of Atomic Radiation. It is published, at the request of the Acting Secretary of the Committee, to help arouse and sustain interest in this most important and immediate problem. The readers of the Journal are again invited to address letters to the editor discussing the effects of atomic radiation on man, and the possible actions which may be taken to control and to counteract such effects.

The Committee has directed its statement primarily to radiologists and others who may use x-rays on human subjects. As a group, human geneticists are probably better able than any other group, to appreciate the importance of the problem. It is their obligation to be fully informed about the possible dangers of atomic radiations to man, and to exert every effort to educate others. It is the geneticists obligation to encourage discussion of this problem by specialists in all areas related, no matter how remotely, to the physical, chemical, biological, and sociological control and exploitation of this source of energy.

ARTHUR G. STEINBERG

INTRODUCTION

THE UNITED NATIONS GENERAL ASSEMBLY, being aware of the problems in public health that are created by the developments of atomic energy, established a Scientific Committee on the Effects of Atomic Radiation. This Committee has considered that one of its most urgent tasks was to collect as much information as possible on the amount of radiation to which man is exposed today, and on the effects of this radiation. Since it has become evident that radiation due to diagnostic radiology and to radio-therapy constitutes a substantial proportion of the total radiation received by the human race, the Committee considers it desirable to draw attention to information that has been obtained on this subject.

Modern medicine has contributed to the control of many diseases and has substantially prolonged the span of human life. These results have depended in part on the use of radiation in the detection, diagnosis and treatment of disease. There are, however, few examples of scientific progress that are not attended by some disadvantages, however slight. It is desirable therefore to review objectively the possible present or future consequences of increased irradiation of populations which result from these medical applications of radiation.

GENERAL SURVEY OF THE IRRADIATION OF HUMAN BEINGS

Man has always been exposed to some irradiation from natural sources. To this has now been added, as a result of modern discoveries and the applications of ionizing radiation and radioactivity, certain forms of artifical irradiation.

Natural irradiation is due to:

(1) Cosmic radiation,

(2) "Background" gamma radiation from radioactive substances present locally in the earth, rock or building materials, and from disintegration products of radon in air,

(3) Radiations emitted from natural radioelements such as potassium 40, radium, radon and carbon 14 which are incorporated in the body.

The amount of this natural radiation varies with locality, but has been estimated as usually delivering between 70 and 170 mrems per year to the gonads. Of this total, the major contributions are of about 45 per cent from local gamma radiations, 30 per cent from cosmic rays and 20 per cent from body potassium 40.[1]

Artificial irradiation is derived from:

(1) The contamination of the environment, the atmosphere, or water by radioactive waste from atomic industries or from users of radioelements;

(2) The radioactive fallout, at greater or lesser distances from the source, or radioactivity resulting from the explosion of nuclear devices;

(3) The occupational exposure of certain groups of workers: medical practitioners, radiologists, dentists, nurses, atomic energy workers, uranium or thorium miners, and the industrial or scientific users of radiation generators or radioactive isotopes;

(4) The medical use of X-rays, other ionizing radiations and radioelements in the detection, diagnosis, investigation and treatment of human diseases;

(5) The use of certain devices which emit radiation, such as television receivers, watches with luminous dials, and the X-ray generators used for the purpose of fitting shoes.

The amount of artificial radiation must vary considerably in different countries and we have inadequate information as to the over-all significance of these factors. In certain countries where estimates have been made, it appears that the greatest gonad irradiation of the population is due to diagnostic radiological procedures, the amount from this source about equalling that from all natural sources in certain instances. The total present contribution from occupational exposure, from the products of atomic industries from radiotherapy and from the radiating devices mentioned above is likely to be very considerably smaller. That from radioactive fallout to the gonads appears at present to be in the region of 1 per cent of the natural gonad irradiation in most areas.[2]

Both the magnitude and the significance of these various sources are under review by the Committee. Since medical irradiation accounts for a substantial if not the major proportion of all artificial exposure, it is important that its magnitude should be known accurately for different countries and circumstances. The possibility of

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[1] From the reports sent by India, Sweden, the United Kingdom and the United States of America.

[2] According to the reports sent by the United Kingdom and the United States of America.

making such an assessment depends upon the help of the medical profession, and particularly on the adequacy and availability of records kept by doctors, dentists and organizations responsible for the use of ionizing radiation.

RADIATION HAZARDS

The medical use of radiation is clearly of the utmost value in the prevention, diagnosis, investigation and treatment of human disease, but the possible effects of this irradiation of individuals require examination.

Generally speaking, the irradiation of living beings may produce radiobiological effects either on the irradiated individual himself or, through him, on his descendants; the former being termed somatic and the latter genetic effects. Somatic effects vary according to the different organs or tissues affected, and range from slight and reversible disturbances such as cutaneous erythema to the induction of leukaemia or of other malignant diseases. The possible reversibility of the somatic effects of radiation received in small doses or at low dose rates encourages the belief that there are permissible doses of radiation which will not cause completely irreversible or significant somatic damage. The threshold for occasional somatic damage may, however, prove to be low. In the case of genetic effects, on the other hand, there may be no threshold. These effects increase with a frequency corresponding to the total amount of radiation received by the germinal tissues, and in the great majority of cases, are adverse.

Many other factors complicate the interpretation of radiobiological effects. The differences between whole and partial body radiation, between a single exposure and continuous irradiation, or between the effects of different types of radiation are still imperfectly understood. Biological differences in the radiosensitivity of various tissues, or of the tissues of people of different age or sex, obviously influence the nature of radiation hazards. It is clear, however, that any radiation of gonads, and any substantial irradiation of other tissues, involve a chance of significant damage which requires assessment.

GENERAL RECOMMENDATIONS REGARDING THE MEDICAL AND OCCUPATIONAL IRRADIATION OF HUMAN BEINGS

The Radiological Profession, through the International Commission on Radiological Protection,[3] has undertaken a valuable and responsible duty in defining maximum permissible limits of exposure for the main radiation hazards.

The establishment of these maximum permissible levels for those who are occupationally exposed to radiation depends on the view that there are doses which, in the light of our present knowledge, do not cause detectable somatic injury in the individual irradiated; and on the consideration that the number of individuals concerned is small enough for the genetic effects on the whole population to be negligible. For the gonads, or for irradiation of the whole body, the levels are such as to exclude doses greater than 0.3 rem in any week or 3.0 rem in any 13 weeks, or a sustained irradiation rate greater than 5 rem per year. These values imply that no total dose

[3] See the report of the International Commission on Radiological Protection, published in the *British Journal of Radiology*—Supplement 6, of December 1954, in the *Journal Francais d'electroradiologie*—No. 10, of October 1955, etc.

of over 50 rem will have been received by the gonads by the age of 30, or of over 200 rem by the whole body by the age of 60, in any occupationally exposed person.[4]

As regards irradiation of the whole population, it is considered prudent to limit the average dose to germinal tissues from artificial sources to the order of magnitude of that received from all natural sources.

In considering the extent to which the population is irradiated for medical purposes, it is essentially the genetic hazard which is involved although it seems possible that in certain circumstances somatic injury may occur occasionally after low doses of radiation. Otherwise, the relevant dose is that indicating the mean gonad irradiation among the population as a whole up to the end of the average reproductive period.

The extent of such genetic irradiation from diagnostic procedures has been found to be equal to at least 100 per cent of all natural radiation in two countries,[5] and that from a third equalled at least 22 per cent of this figure.[6] Even before obtaining more exact values for these and other countries, it is clear that the exposure can be substantial in countries with extensive medical facilities, and that it is essential to consider any ways in which this exposure could be reduced without detriment to the existing or developing value of medical radiology.

The Committee is therefore anxious to obtain the help of radiologists in suggesting through appropriate governmental channels any methods by which this total exposure could be reduced and in estimating the amount of reduction that might be expected from any such methods. In particular it would be valuable to know how much the radiation to the gonads could be reduced.

(a) by improved design or shielding of equipment,

(b) by fuller training of any individuals using radiographic or fluoroscopic equipment,

(c) by any local shielding of the gonads that is practicable, especially during abdominal or pelvic examination,

(d) by the use of techniques involving radiography rather than fluoroscopy when full information can be obtained by this means,

(e) by improvement of administrative arrangements designed to obviate unnecessary repetition if identical examinations of the same subject,

(f) by a general study of certain medical conditions such as that of peptic ulcers, to identify the circumstances in which the establishment of a radiological diagnosis has or has not a definite influence upon the treatment or prognosis given.

SUMMARY

1. The Scientific Committee of the Effects of Atomic Radiation established by the United Nations General Assembly accepts the view that the irradiation of human beings, and especially of their germinal tissue, has certain undesirable effects.

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[4] See the report of the International Commission on Radiological Protection, published in the *British Journal of Radiology*—Supplement 6, of December 1954, in the *Journal Francais d'electroradiologie*—No. 10, of October 1955, etc.

[5] Sweden, United States of America.

[6] United Kingdom.

2. Information received so far indicates that, in certain countries (Sweden, United Kingdom, United States of America), by far the most important artificial source of such irradiation is the use of radiological methods of diagnosis and that this may be equal in importance to radiation from all natural sources. It is possible that such radiation may be having a significant genetic effect on the population as a whole.

3. The Committee is fully aware of the importance and value of the medical use of radiations but wishes to draw the attention of the medical profession to these facts and to the need for a more accurate estimate of the amount of exposure from this source. The help of the medical profession would be most valuable to make it possible to obtain fuller information on this subject.

4. The Committee would be particularly grateful for information through appropriate governmental channels on ways in which the medical irradiation of the population can be reduced without diminishing the true value of radiology in diagnosis or treatment.

The Laboratory Detection of Heterozygotes[1]

DAVID YI-YUNG HSIA

Department of Pediatrics, Northwestern University Medical School; and the Children's Memorial Hospital, Chicago

THE FUNDAMENTAL DISCOVERY that the erythrocytes of patients with sickle cell anemia contain hemoglobin with a significantly different isoelectric point from that of normal individuals was reported in 1949 by Pauling, Itano, Singer, and Wells (83). This provided the first positive evidence that adult human hemoglobin exists in more than one molecular form. It provided support for the concept that many hereditary diseases of a biochemical nature may be caused by genetically determined abnormalities of protein synthesis and for the concept that the asymptomatic carriers of such traits should be detectable by means of laboratory tests.

If an individual is heterozygous for a given trait, he carries one "normal" and one mutant gene, and the molecules derived from the mutant gene may be expected to differ from those derived from the "normal" gene within the same individual. Such individuals might appear to be asymptomatic. Careful physical and biochemical studies, however, might reveal minor departures from the norm. Studies at a molecular level are most likely to reveal the abnormality. The distribution of such molecular differences among members of a family can be represented just as can the distribution of a gene in the familiar diagram of pedigrees.

In the past, Neel (75, 77, 79, 80) has called attention to a number of diseases where the "genetic carriers" may be detected by minor clinical abnormalities. The purpose of the present paper is to review the evidence for the detection of heterozygotes in the laboratory, and to see whether this approach might be extended to some of the other hereditary diseases in man.

GENERAL CONSIDERATIONS

It might be appropriate to begin by discussing what types of evidence are needed to establish heterozygosity. In the first place, it is essential to define in genetic terms the exact mode of inheritance of each condition. When this is known, it is possible to identify the individuals who are most likely to be heterozygotes within the family and select them for appropriate testing. In simple recessive inheritance, the parents would be the most suitable subjects. In the case of dominant inheritance with incomplete penetrance, as in gout, or late onset, as in Huntington's chorea, the parents, sibs, and offspring may be studied. In sex-linked recessives, the mother would be the easiest subject to study. It is usually better to avoid the more distant relatives since the heterozygotes are less frequent among that population. If available, the observations should be repeated on more than one pedigree and in as many close relatives as are accessible.

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Next, it is important to be sure that the methods used are adequate for the purpose. The laboratory techniques should be tested first against known standards, and then with samples taken from patients. The degree of sensitivity of the method at the upper and lower limits should be known and the most useful range should be selected for the experiment. This test should be applied to an adequate group of normal controls, preferably of all ages, and of both sexes, so that normal variations can be taken into account in the analysis.

It is assumed that the changes which are chemically closest to the principal metabolic defect would be looked for first. For instance, in Wilson's disease with our present knowledge, it would be logical to look for a defect in ceruloplasmin synthesis rather than a disturbance in amino acid excretion. In fact, detection of a change in one of the secondary manifestations without finding a similar change in the principal defect would be suspect. Frequently, the changes cannot be found by ordinary means. In such situations, it is sometimes useful to place additional stress on the metabolic system involved by some type of tolerance test. This has been helpful in detecting heterozygotes in galactosemia and phenylketonuria.

Finally, it is important to establish that a significant difference exists between the measurements in the heterozygous individuals as compared with normal controls. This should be done not only by statistical analysis, but also by ruling out possible normal physiological or chemical variables definitely.

In human material, it is frequently not possible for any one group to get enough data to establish the detection of a heterozygote. For instance, electroencephalogram abnormalities are found in one or both parents of epileptics, but also in 16 per cent of normal controls. Similarly, achlorhydria is a fairly reliable prodrome of pernicious anemia, but is also found in 10 to 15 percent of the normal population in the advanced age group. However, if the data are published in a useful form so that other investigators can add to the information a solution may be reached none the less. As a general rule, the following types of information should be included in the report: (1) detailed genetic information on the family or families studied; this can usually best be done by including a family diagram or pedigree; (2) adequate clinical descriptions not only of the affected individuals, but also of their relatives even if they appear to be free of symptoms; and (3) outline of the laboratory methods used so that subsequent workers may use the same techniques. It will be obvious from the present survey that previous publications have lacked uniformity in standards for properly presenting the evidence and this has frequently hindered progress in this rapidly developing field of human genetics.

CONDITIONS WHERE ABNORMALITIES HAVE BEEN NOTED IN THE HETEROZYGOTE

It should be borne in mind that the expressivity of genes varies among individuals. This means that the abnormalities reported cannot invariably be detected in every heterozygote nor in every pedigree studied. A review of this nature must of necessity take a broad viewpoint and include all evidence that appears to be significant.

Conditions where abnormalities have been noted in the heterozygote can be divided into three groups:

GROUP A: CONDITIONS FOR WHICH THE EVIDENCE APPEARS TO BE RELIABLE AND HAS RECEIVED INDEPENDENT CONFIRMATION

1. *Afibrinogenemia*—The principal defect in this condition is a marked decrease of fibrinogen in the plasma which results in a profound disturbance in the blood clotting mechanism. The condition frequently arises in offspring of cousin marriages and is believed to be transmitted as a rare recessive.

Isolated instances of genuine fibrinogenopenia have been reported among near relatives of patient with congenital afibrinogenemia. In 1938, MacFarlane (65) found that the father of his patient had a plasma fibrinogen level of only 75 mgm. per cent (normal, 200–400 mgm. percent). The following year, Schonholzer (100) showed that a sister of his patient had a level of 130 mgm. percent with no clinical symptoms. More recently, Prentice (88) and Lawson (63) have reported fibrinogen levels of 120 mgm. per cent and 150 mgm. per cent in the plasma of a maternal aunt and the mother of each of two separate patients. Despite variations in the technique for determining fibrinogen in the plasma, these levels appear to be sufficiently below the normal level to be significant.

Frick and McQuarrie (39) have undertaken fibrinogen determinations in 12 relatives of a boy with afibrinogenemia. Fibrinogen was determined by the precipitation of fibrin and micro Kjeldahl nitrogen determination on the fibrin clot. By this method the normal range of variation is 250 to 400 mgm. per cent. These authors found that both parents and two siblings had fibrinogen levels below 200 mgm. per cent, while a third sibling had a concentration of 248 mgm. per cent. With only one exception, the seven aunts and uncles tested were hypofibrinogenic, although other tests for hemostasis showed no gross abnormalities.

2. *Cystic Fibrosis of the Pancreas*—This is a hereditary condition in which the clinical evidences of the celiac syndrome, resulting from pancreatic exocrine insufficiency, are combined with the presence of severe pulmonary disease, and disturbances in the secretion of the sweat and salivary glands. It is believed to be transmitted by an autosomal recessive gene.

Early studies failed to demonstrate any disturbances in exocrine or pulmonary function among parents and near relatives of known cases. In 1955, di Sant'Agnese (98) found that the same elevation of electrolytes in the sweat seen in the affected children, could sometimes be found among their parents and sibs. More recently, Shwachman and Steinberg (102) have confirmed this finding in a much larger group of families. In general, the concentration of electrolytes in the sweat of the heterozygotes falls between the range for children with cystic fibrosis and that for normal controls with considerable overlap in both directions.

3. *Gout*—Gout is a hereditary constitutional disease, occurring predominantly in males, characterized by recurrent acute arthritis. The articular inflammation may become chronic and may be associated with deposits of sodium urate (tophi) which may be found in many tissues.

In 1948, Smyth, Cotterman and Freyberg (106) examined 87 symptom-free adult blood relatives of gouty male patients in 19 families. They found that in 11 of these families, hyperuricemia was present in at least one member other than the index patient. Of 48 male relatives, 13 had serum urate levels of 6 mgm. per cent or more,

and of 39 female relatives, 11 had levels of 5 mgm. per cent or more. Thus, 28 per cent of the 87 members of these families showed asymptomatic hyperuricemia. They concluded that hyperuricemia is due to a single autosomal gene, whose presence in the heterozygous condition is detectable in a large proportion of cases by an elevated uric acid level in the blood, and in a much smaller proportion of cases by the clinical symptoms of gout. Essentially, the same findings have been reported by Stecher, Hersh and Solomon (110) in a larger group of families.

4. *Hereditary elliptocytosis*—Motulsky and his coworkers (72) have suggested that hereditary elliptocytosis should be included in the group of hereditary hemolytic diseases associated with red cell shape anomaly. The gene for elliptocytosis, like that for sickling, thalassemia, and hereditary spherocytosis, is detectable in the heterozygous condition. The homozygotes for the "sickle cell gene" have sickle cell anemia, those homozygous for the "thalassemia gene" have thalassemia major, while their parents are heterozygous for the sickling or thalassemia genes respectively. A double dose of the mutant gene results in severe hemolytic disease, while a single dose in the heterozygote results in mild but detectable blood changes. It may be expected that the same would be true for the gene for elliptocytosis. This gene, however, is less frequent in the population, hence homozygosity for elliptocytosis is expected to occur only rarely. Up to the present, only two possible examples of homozygosity have been reported in the literature (14, 124). Both have been characterized by marked hemolysis associated with microspherocytosis and microelliptocytosis.

The heterozygote for elliptocytosis will frequently be free of clinical signs and symptoms. However, laboratory studies will reveal: (1) elliptocytosis, (2) reticulocytosis, (3) slight elevations of serum bilirubin, (4) increased excretion of urobilinogen in the stools, and (5) changes in osmotic and mechanical fragility of the red cells. Homozygosity would presumably always be associated with marked hemolysis and present a different clinical and laboratory picture.

Motulsky et al. (72) have suggested that this gene may occur in combination with that for sickle cells or the one for thalassemia and result in a clinical picture indistinguishable from that of homozygous elliptocytosis. Further studies are needed to clarify this interesting point.

5. *Hereditary spherocytosis*—The studies of Race (91) and Young, Izzo and Platzer (125) indicate that hereditary spherocytosis is probably inherited as a mendelian dominant, with one half of the offspring of an affected parent being similarly affected. The heterozygotes are usually identifiable. Many show signs of anemia, mild icterus, and evidence of increased destruction of erythrocytes as demonstrated by increased fecal urobilinogen excretion. Other heterozygotes may show no clinical signs and symptoms. However, careful studies by osmotic and mechanical fragility will frequently reveal an abnormality. The latter test is particularly useful after the red cells have been incubated for 24 hours at 37 degrees C. in vitro. The homozygous form of hereditary spherocytosis has not yet been demonstrated with certainty, although its occurrence has been suspected in families studied by Race (91) and Bernard and his coworkers (13).

Young (126) has called attention to a number of patients with spherocytosis where both parents on repeated testing had no demonstrable hematologic abnormalities.

Normal findings were also obtained from all other available relatives of these patients with one highly significant exception. An infant sibling of one of the patients was found to have hereditary spherocytosis. One wonders if these may represent fresh mutations, or whether there may be a recessive type of spherocytosis in addition to the more common dominant form. This also raises the important question as to whether, despite these refinements, our laboratory methods are good enough to identify all the heterozygotes for hereditary spherocytosis.

6. ***Hypophosphatasia***—Patients with this condition show spontaneous shedding of teeth prematurely and characteristic bone changes including genu valgum, bowing of the femur and tibia, enlarged wrists, and poor mineralization of the long bones, ribs, jaw, and teeth. All show a marked deficiency in alkaline phosphatase in both the plasma and tissues. Steinberg (113) has suggested that the condition could be transmitted as a rare recessive. However, a higher frequency of affected children among the last born suggests that hypophosphatasia can, at least in part, be the result of a changed intrauterine environment.

Two types of changes have been noted among presumed heterozygotes. Sobel, Clark, Fox, and Robinson (107), Dent and Harris (28) and Steinberg (113) have all found low alkaline phosphatase activity without bone changes in one or both parents. The latter found that 15 out of 22 parents (about 70 per cent) and three out of seven healthy sibs showed detectably reduced plasma alkaline phosphatase activity.

Early in 1955, McCance, Morrison, and Dent (66), and Fraser, Yendt, and Christie (37) independently reported the presence of phosphoethanolamine in the urine of patients with hypophosphatasia. The metabolite was identified by means of paper partition chromatography, and was not found in the urine of normal controls. Family studies have revealed lesser amounts of phosphoethanolamine in the urine of asymptomatic parents, siblings, and near relatives of index cases (37, 30, 67).

7. *Idiopathic hemochromatosis*—Hemochromatosis is a chronic disease characterized by the deposition of iron in body tissues with eventual fibrosis and functional insufficiency of organs involved. Its occurrence among siblings, uniovular twins, and among the offspring of a consanguineous mating suggest that it is a genetic disease.

Finch and Finch (33) have performed serum iron determinations on 50 siblings and children of 12 proven adult patients with hemochromatosis. They found that 20 per cent of these relatives had serum iron values of in excess of the upper normal limit of 150 μgm. per cent. In three of the asymptomatic siblings with elevated serum iron values, increased iron stores were demonstrated by the phlebotomy technique (32). The same type of changes in serum iron levels have been noted by Debre and his coworkers (27).

8. *Idiopathic hypercholesteremia*—In a study of two families with idiopathic hyperlipemia, Adlersberg (3) has found both this error of lipid metabolism and idiopathic hypercholesteremia. A study of these "mixed" families suggest that both disorders may be closely related, and that one may represent a variant of the other. Although this is an attractive hypothesis, the biochemical disturbances in the two diseases are quite distinct. They will, therefore, be treated as separate entities in the present discussion.

Adlersberg and his coworkers (2, 16, 99) and Stecher and Hersh (111) have sug-

gested that the elevation of cholesterol is due to a simple dominant gene. In 1948, Fliegelman, Wilkinson, and Hand (34) investigated 270 persons in a large kindred over four generations. They presented evidence that essential hypercholesteremia is transmitted as an incomplete dominant trait. Xanthoma tuberosum multiplex represents the homozygous state of the inherited factor which when heterozygous produces only hypercholesteremia. Herndon (49) has also suggested that minor skin manifestations, such as xanthelasma palpebrarum and small nodules of the fingers, may also represent the heterozygous state of the gene.

9. *Labile (Ac-Globulin) Factor deficiency—(Parahemophilia)*—In 1947, Owren (82) reported extensively on the behaviour and properties of a plasma factor necessary for the normal conversion of prothrombin to thrombin and described the first case of hemorrhagic diathesis due to deficiency of this factor. Such patients have a normal concentration of prothrombin but lack Labile (Ac-Globulin) factor, a defect which can be readily corrected by the addition of fresh plasma.

The condition appears to be transmitted by a single recessive gene. Kingsley (59) has reported on a pedigree where both parents had normal "prothrombin times", but reduced concentration of labile factor in the plasma as measured by the method of Stefanini (112). All nine of the children were studied. Three had parahemophilia with bleeding, four had diminished labile factor but no bleeding, and the other two were normal. Five of the 15 grandchildren had deficiencies of labile factor, but only one of the remaining 10 was an offspring of an abnormal parent. Similarly, Owen and Cooper (81) and Sacks and Raccuglia (97) have shown that although the parents of patients have normal "prothrombin time", a marked deficiency of Ac-Globulin can be demonstrated when the residual Ac-Globulin of fresh serum was determined after spontaneous coagulation or after treatment of their plasma with thrombin.

This raises the point that the asymptomatic cases of parahemophilia described by de Vries, Matoth, and Shamir (120), Alexander, and Goldstein (5), and Stohlman, Harrington, and Maloney (114) might in reality be heterozygotes for the trait rather than homozygotes with mild manifestation as has had previously been believed.

10. *Nephrogenic diabetes insipidus*—This is a congenital disease in which the renal tubules fail to respond to antidiuretic hormone. As a result, there is continual excretion of a large volume of dilute urine, and excessive thirst. If sufficient water is not consumed, the patient will rapidly become dehydrated. The condition is believed to be transmitted by a single recessive sex-lined gene.

Both Walker and Rance (121) and West and Kramer (122) have noted excessive thirst and passing of large volumes of urine during early life in the mothers of patients with this condition. More recently, Carter and Simpkiss (21) have reported on four families with this condition where the women who are likely to be heterozygous frequently give a history suggestive of a mild form of diabetes insipidus. Measurements of the specific gravity of the urine after withholding fluid intake for 12 hours appears to give reasonably good discrimination between normals and presumed heterozygotes.

11. *PTC (Plasma thromboplastin component) deficiency*—It is now well established that PTC, also known in the British literature as Christmas factor, is essential for the formation of blood thromboplastin. Absence or marked diminution of PTC

causes a severe bleeding syndrome clinically indistinguishable from classical hemophilia. In the laboratory, the two conditions can be differentiated by: (1) the partial thromboplastin time (60); (2) the thromboplastin generation test (15); and (3) the inability of the patient's plasma to correct the clotting defect of known hemophilic blood with normal and hemophilic plasma. Like hemophilia, the condition is transmitted as a sex-linked recessive.

PTC was diminished among carriers in at least four families with Christmas disease. Rosenthal (96) has reported on a PTC carrier with a heparin clotting time of 35 minutes and serum prothrombin time of 13 seconds. Her plasma was less effective than normal plasma in correcting the clotting defect in her son. Brinkhous and his coworkers (18) have reported a similar situation; the mother was found to have a partial PTC deficiency. Her clotting time was 12 minutes. The prothrombin (two stage) was 100 per cent of normal, and the AHF (antihemophilic factor) was 93 per cent. Prothrombin utilization was impaired, with 56 per cent prothrombin remaining in the serum after two hours. Ramot, Angelopoulos, and Singer (92) have described an asymptomatic mother who showed a definite decrease of thromboplastin generation although the serum prothrombin time was normal. The same findings were noted among three male members of a second family, but they also showed mild hemorrhagic manifestations. It is interesting to note that the mother of a third patient failed to show any decrease of PTC by the thromboplastin generation test.

12. *Sickle cell anemia*—It has been shown that sickle cell anemia, a condition probably created by homozygosity of a single gene (12, 78), is associated with the presence in the red cells of a hemoglobin different from normal adult hemoglobin (83). This can be shown by striking differences between the solubilities of the reduced forms of the two hemoglobins and by changes in electrophoretic measurements in the pH range between 5.5 and 8.0. From the genetic point of view, it has been shown that: (1) the normal adult has only normal hemoglobin; (2) the heterozygote with one normal and one sickle cell gene has less than half of sickle cell hemoglobin and the remainder as normal adult hemoglobin; and (3) the sickle cell anemia patient, homozygous for the sickle cell gene, has primarily sickle cell hemoglobin.

More recently, a number of other abnormal hemoglobin disturbances have been described. It has also been shown that an individual may be heterozygous for thalassemia or hereditary spherocytosis and for one of the abnormal hemoglobins. These heterozygotes can be identified chemically by undertaking appropriate tests (22).

13. *Stable (Serum prothrombin conversion accelerator) factor deficiency*—Patients with this defect show a prolonged prothrombin time by the unmodified one stage test, which can be corrected by the addition of a small amount of normal serum or a partially purified preparation of the stable factor. The parents of patients with SPCA deficiency are presumably heterozygotes.

Quick, Pisciotta, and Hussey (90) have reported three families in which either the parents or children of patients with SPCA deficiency show a slight prolongation of prothrombin time, which can be corrected by the addition of stable factor. Frick and Hagen (35) have also reported that the mother and two siblings of his patient show normal prothrombin time with moderate delay of prothrombin conversion.

It is interesting to note that the latter family was related to one of the families reported by Quick.

Recently, Seegers and his associates (101) have reported evidence interpreted as showing that SPCA is an altered form of prothrombin. If this is confirmed, it may turn out that "SPCA deficiency" is in reality a hereditary defect of prothrombin.

14. *Thalassemia*—Neel and Valentine (76) and others (103, 104) have postulated that thalassemia major (Cooley's anemia) represents the homozygous state for the thalassemia gene, whereas the heterozygous condition results in thalassemia minor. Individuals in the latter group are usually free of symptoms, but show slight hematologic abnormalities, such as mild anemia, hypochromia, anisocytosis, and poikilocytosis. Chemically, they fail to show an increase of fetal hemoglobin (Hgb. F), but frequently will show the same lack of iron-binding capacity which is characteristically seen in thalassemia major (105). This would fit the concept that the basic defect in thalassemia seems to be quantitative inability to incorporate iron into the hemoglobin molecule and perhaps an inability to form adult hemoglobin itself.

Clinical "atypical hemolytic syndromes" may be found in individuals who are heterozygous for both the thalassemia gene and the gene responsible for the formation of Hgb. S, C, or E. These individuals show not only the abnormal hemoglobin in question, but also Hgb. F in their blood (115).

GROUP B: CONDITIONS WHERE THE EVIDENCE APPEARS TO BE RELIABLE, BUT HAS NOT BEEN CONFIRMED TO DATE

15. *Adrenal hyperplasia*—The primary metabolic defect in virilizing adrenal hyperplasia consists of failure of the adrenal cortex to synthesize Compound F. Bongiovanni and his coworkers (17) have shown that 3 alpha-17 alpha-20 alpha pregnanetriol is the steroid found in greatest quantity in the urine of affected individuals and furthermore, that the administration of ACTH to patients with adrenal hyperplasia caused a rise in urinary pregnanetriol frequently of greater magnitude than the increase of 17 ketosteroids. The condition is probably transmitted by a single autosomal recessive gene.

Childs, Grumbach, and Van Wyk (23) have made measurements of pregnanetriol in the urine of 20 parents of children with adrenal hyperplasia before and after stimulation with ACTH, to determine whether a rise in this metabolite would appear. These were compared with 18 normal controls. The difference between the increments of parents and controls was significant at the .05 level, but there was considerable overlap of the values for the two groups.

16. *Cystinuria*—Harris and his coworkers (46) have suggested that there may be two phenotypes for cystinuria. Patients belonging to Phenotype 1 show greatly increased excretion of cystine, lysine, arginine, and ornithine in the urine and occasionally develop cystine stones. Those in Phenotype 2 show only moderate increases of cystine and lysine in the urine and rarely form stones. The families with cystinuria fall into two groups. In one, there is a complete absence of Phenotype 2, and the segregation of Phenotype 1 makes it consistent with the hypothesis that it represents the homozygote for a rare recessive gene. In the other group of families, Phenotype

2 is frequently found. In these, the distribution of the two abnormal phenotypes is consistent with the hypothesis that Phenotype 1 represents the homozygote and Phenotype 2 the heterozygote of a rare abnormal gene. These studies were primarily done using paper partition chromatography techniques.

17. *Congenital hypothyroidism with goiter*—Goitrous cretinism occurring sporadically outside areas of endemic goiter is usually hereditary in nature. Most of the patients develop myxedema or goiter before the age of three and can be identified by the typical coarse, rather ugly facies, superclavicular pads, scanty eyebrows, and dry, lusterless hair. All of the patients are dwarfed and mentally defective. However, in none of the patients are the signs of hypothyroidism as gross as they would have been in untreated sporadic or endemic cretins of comparable age.

The condition represents an inability to utilize inorganic iodide properly. Very little labelled free mono- or di-iodotyrosine appears in the serum of a normal individual, following the ingestion or injection of I^{131}, but Stanbury and his coworkers (108) showed that both labelled mono- and di-iodo-tyrosine were detected in large amounts in the serum of a patient with hypothyroidism and familial goiter. More recently, he and his coworkers (109) have found that when mono- and di-iodo-tyrosine is injected intravenously, they appear almost entirely unchanged in the urine of these patients. Since there was no evidence for any deiodination, it would appear that the condition arises as a result of the absence of the deiodinase.

Five relatives (four with goiter) of one of the patients with congenital goiter and hypothyroidism were studied after the administration of I^{131} labelled di-iodo-tyrosine. It was found that although these patients deiodinated di-iodo-tyrosine, a larger fraction of the injected dose was excreted unchanged in the urine than in a group of 15 controls (109).

18. *Galactosemia*—Holzel and Komrower (54) undertook galactose tolerance tests among parents, sibs, and near relatives of five families with known cases of galactosemia. Adults were given a total dose of 40 Gm. of galactose, older children 1.25 Gm. per kg., and infants 1.75 Gm. per kg. body weight. Galactose in the blood was determined by the method of Maclagan (68) at ½, 1, 1½, and 2 hours after the test dose. The investigators found the response to be abnormal in a number of the relatives tested, but this was not a consistent finding among all the individuals who should be heterozygotes. They concluded that abnormal galactose tolerance without clinical manifestations is inherited as a heterozygous character while clinical galactosemia must be transmitted as a homozygous recessive gene.

Isselbacher and his coworkers (55) have recently demonstrated that the primary metabolic defect in galactosemia is a decrease of the enzyme, P-Gal-uridyl transferase. However, they have been unable to show a decrease of this enzyme in the red cells of parents of known galactosemics (6). In view of Holzel and Komrower's findings, which are actually one step further removed from the basic defect, it appears likely that some decrease of this enzyme will eventually be found in such individuals. Most probably, the techniques for the assay of P-Gal-uridyl transferase can be improved so that small changes in the heterozygote will become detectable.

19. *Phenylketonuria*—The molecule whose dysfunction is responsible for the hereditary disease phenylketonuria is the liver enzyme concerned with the oxidation of

phenylalanine. Hsia, Driscoll, Troll, and Knox (51) have shown, by means of phenylalanine tolerance tests, that known heterozygotes of phenylketonuria have reduced capacities for metabolizing phenylalanine. Plasma levels of L-phenylalanine were determined by the phenylethylamine method of Udenfriend and Cooper (117) one, two, and four hours after an oral dose of 0.1 Gm. per kg. body weight of L-phenylalanine in 19 parents of proven phenylketonurics and an equal number of normal controls. During the test, the phenylalanine levels in the heterozygotes were on the average about twice those of the controls at each of the points on the curve. A similar elevation was noted in three of six normal siblings of patients with phenylketonuria.

More recently, Hsia, and Driscoll (52) have demonstrated a difference between the fasting L-phenylalanine levels of heterozygotes for phenylketonuria and normal controls. Although there is a 30 per cent overlap between the two groups, the differences are significant (t equals 5.25, P less than 10^{-6}). This suggests that the phenylalanine load merely brings out the differences between the two groups in a more striking manner.

GROUP C. CONDITIONS WHERE SOME SUGGESTIVE EVIDENCE HAS BEEN PRESENTED

20. *Diabetes Mellitus*—There is universal agreement that there is a large hereditary component in the causation of diabetes mellitus, but disagreement arises when an attempt is made to describe how it is transmitted from one generation to the next. Most workers feel that the condition is transmitted as a recessive. There are two types of changes among near relatives of diabetics, however, which are worthy of mention.

In 1934, Pincus and White (87) showed that 14 per cent of a group of near relatives given routine glucose determinations and 25 per cent of those given glucose tolerance tests had abnormally high blood sugar values. These individuals were classified as "future" diabetics on the basis of the Mendelian hypothesis. Follow up studies seem to indicate that most of these individuals have not developed diabetes although the abnormal glucose tolerance curves have persisted (123). Furthermore, in a more recent study, abnormal glucose tolerance tests have been noted among one or both parents of juvenile diabetics. This would seem to suggest that such individuals could be heterozygotes for diabetes mellitus.

More recently, Fajans and Conn (31) have undertaken combined cortisone-glucose tolerance tests to study the heredity of diabetes mellitus. In a survey involving 152 relatives, they found that 19 per cent showed abnormal glucose tolerance tests as compared with only one among 50 normal controls. After the administration of 50 mgm. of Cortisone eight hours before the test, this incidence was increased to 24 per cent, while again only one of 37 controls showed this abnormality.

21. *Gaucher's disease*—Gaucher's disease is a hereditary disorder of lipid metabolism characterized by the accumulation of the cerebroside kerasin in the cells of the reticuloendothelial system. The condition is due to an autosomal recessive gene.

Groen (45) has reported the presence of Gaucher-like cells in the sternal marrow of the father of two children with typical Gaucher's disease. These are described as reticulum or stem cells, but the faintly stained protoplasm was nonhomogeneous in character and resembled in its structure compressed tissue paper. These findings

have not been confirmed among several parents studied by Crocker (26) and these cells have also occasionally been seen in apparently normal individuals.

Uzman (119) has recently isolated a new water-soluble glycolipid from the spleens of patients with Gaucher's disease. It would be interesting to undertake similar studies on parents of such patients and see if this compound might be in any way related to the Gaucher-like cells in the marrow.

22. *Glycogen storage disease* (*Von Gierke's disease*)—This rare congenital disorder of carbohydrate metabolism occurring in infants and young children is characterized by the storage of abnormally large amounts of glycogen not only in the liver, but also in the kidneys, heart, skeletal muscle and other organs. A deficiency of the enzyme glucose-6-phosphatase is responsible for these metabolic changes. The condition is probably transmitted as an autosomal recessive.

Kapila, Kaul, and Chatterjee (56) have reported a family with this disease where the father, mother, and the siblings showed a borderline response of blood glucose levels to 0.25 ml. of adrenalin intramuscularly. One of the siblings also showed a flat oral glucose tolerance curve. While this probably does not represent a definitive difference, it is sufficiently suggestive to warrant further study.

23. *Hemophilia*—Classical hemophilia is one of mankind's oldest and most extensively studied diseases. Various workers have attempted to detect abnormalities in the mother. Merksey and MacFarlane (70) tried to show a coagulation defect among known female carriers in a large group of hemophilic families. They found the changes to be too inconsistent to be clinically useful. Similarly, Biggs and Douglas (15) could demonstrate no changes with the thromboplastin generation test among normal mothers of known hemophiliacs. Brinkhous and his coworkers (18) have also failed to show any decrease of AHF (anti-hemophiliac factor) among presumed heterozygotes. Recently, Margolius and Ratnoff (70) have reported similar negative results.

In 1953, Graham, McLendon, and Brinkhous (44) described one family with mild hemophilia, a presumed allelic form of the disease, where the AHF as measured by the simplified method of Langdell, Wagner, and Brinkhous (60) was reduced to levels of less than 25 per cent of normal. Like classical hemophilia, mild hemophilia is a sex-linked recessive trait. However, roughly half of the heterozygous females were found to have a partial reduction of AHF. These women have a mild tendency to bleed easily and to have menorrhagia.

24. *Hypoglycemosis*—McQuarrie (69) has described a clinical entity characterized by severe persistent hypoglycemia with convulsions which can be successfully alleviated by the use of corticotropins. Anderson and McQuarrie (7) have suggested that hypoglycemosis represents a hereditary metabolic defect and probably is transmitted as an autosomal recessive. They report that two of the parents show abnormal laboratory findings, consisting of an increased response to the insulin sensitivity test.

25. *Idiopathic hypoprothrombinemia*—It is now generally agreed that this condition should be regarded as a separate clinical and genetic entity, which can be differentiated from the deficiency of one of the accessory factors for coagulation. Idiopathic

hypoprothrombinemia is characterized by a tendency to bleed and prolongation of the plasma prothrombin time as measured by Quick's method using acetone-dehydrated rabbit brain as the thromboplastin reagent (89). The prothrombin time cannot be restored to normal by the addition of either fresh deprothrombinized plasma or stored plasma or serum. The condition is inherited as an autosomal recessive.

Several early workers reported a prolongation of prothrombin time without symptoms of bleeding among near relatives of affected patients. Murphy and Clark (74) found that the father of their patient had a prothrombin time of 19 seconds as compared with a normal control of 16 seconds. Giordano (41) found that a father, mother, brother, and sister showed prothrombin times varying between 24 and 63 per cent of normal by the Quick method. Covey, Cohen, and Papps (24) made similar observations on the mother, sister, and the sister's two daughters in another family. Finally, Quick and his associates (90) have published studies on two families with hypoprothrombinemia. In one, all the relatives were found to have normal prothrombin times, while in the other family, the mother, one son, and the daughter of the patient showed prothrombin times of 16 seconds as compared with a normal control of 12 seconds. In this family, the mother and son showed no abnormal bleeding. The daughter, however, had severe menorrhagia at the time of puberty, but it is uncertain whether the coagulation defect played a role. Quick believes that the type of hypoprothrombinemia in the two families can be differentiated by coagulation tests with both lacking free prothrombin, but the former also lacking prothrombinogen. Despite the fact that Quick's plasma prothrombin time is not highly accurate, these changes in possible heterozygotes are worthy of note.

26. *Idiopathic hyperlipemia*—Unlike hypercholesteremia, this condition occurs rarely and the genetics are not complete. Data is available on only four families with idiopathic hyperlipemia. Holt, Aylward, and Timbres (50) studied the blood lipid levels of near relatives of their patient. They found that the father, sister, and one brother had normal levels. The mother showed a total lipid level of 1.43 Gm. per cent and the brother 3.01 Gm. per cent (normal range 0.57–0.82 Gm. per cent) (84). The mother was free from symptoms but the brother was noted to have lipemia retinalis. Bruton and Kanter (19) and Harslof (48) have reported similar increases among near relatives.

27. *Juvenile amaurotic idiocy (Tay-Sach's disease)*—This disease, which is characterized by a progressive degeneration of the ganglion cells in the retina and throughout the central nervous system, is transmitted as a simple recessive. Very little is known about the pathogenesis of the disease process.

Rayner (93) has reported on the presence of lymphocytes in smears of the peripheral blood (7) of four parents of two unrelated cases and in six out of seven normal siblings of one patient. In the same study, four normal spouses of these siblings were found to have normal cytology. Although the significance of this is not clear at present, it appears to be a promising lead for the eventual detection of heterozygotes on a biochemical basis.

28. *Niemann-Pick's disease*—Pfändler (85, 86) has suggested that there may be two forms of this disease. The infant with the "malignant" form may represent the

homozygote and the adult with the "chronic" form may represent the heterozygote. Such heterozygotes are frequently noted to show elevations of various blood lipids. This work certainly needs confirmation.

29. *PTA (Plasma thromboplastin antecedent) deficiency*—Recently, Rosenthal and his coworkers (95) have established a third thromboplastin defect, which they have named PTA deficiency. This defect in coagulation can be corrected by normal serum, but not by barium sulfate treated plasma. Unlike hemophilia, the condition is not sex-linked, and appears to be transmitted by a dominant gene with marked variation in clinical severity.

Rosenthal (96) has reported on a PTA carrier, who is both the mother of a patient and a sister of another patient, who showed an abnormal utilization of prothrombin. Fresh plasma from this carrier failed to correct the clotting defect in her daughter.

30. *Wilson's disease (hepato-lenticular degeneration)*—It is now generally agreed that a defect in the synthesis of ceruloplasmin is the principal disturbance in Wilson's disease, a condition transmitted by an autosomal recessive gene. Detection of the heterozygote has so far been unsuccessful. However, Bearn (11) has recently noted a slight but definite decrease of ceruloplasmin synthesis in an asymptomatic sister of a patient with Wilson's disease, and this may mark the beginning of a new approach. This was done by administering Cu^{64} and measuring the radioactivity of the alpha 2 globulin separated by zone electrophoresis (10). Turpin (116) has reported a similar change among heterozygotes.

It should be pointed out that Uzman and Hood (118) had previously reported persistent amino-aciduria in five asymptomatic members of a family of which four siblings had died of Wilson's disease. These observations have not been confirmed in a larger group of families studied by Bearn (9). This is not surprising in view of the evidence that the amino - aciduria occurs as a secondary effect due to deposition of excessive copper in the proximal tubules. One wonders if Uzman and Hood were dealing with another metabolic defect, which was similar in nature, and also characterized by amino-aciduria.

CONDITIONS WHERE NO ABNORMALITIES HAVE BEEN NOTED IN THE HETEROZYGOTE

No specific abnormalities could be detected in ten conditions as shown in table 1. This may be in part because only minor functional disturbances related to the full disease picture were sought. For instance, the gamma globulin levels in the siblings and parents of children with agamma-globulinemia have been found to be perfectly normal. It may follow that the gamma globulin producing mechanism itself is not disturbed in this defect. A defect causing the absence of plasma cells in these patients (42) may be the actual basis of the disease. In other conditions, the reserve functions of the body might effectively mask the malfunction of a small fraction of abnormal molecules. In fructosuria, an enzyme converting fructose to glucose is presumably disturbed. The normal excess of that enzyme, or the various alternative metabolic routes open to a limited amount of fructose might obviate any spillage of fructose into the urine when only part of the enzyme present is defective.

TABLE 1. CONDITIONS WHERE NO ABNORMALITIES HAVE BEEN NOTED IN THE HETEROZYGOTE

Condition	Characteristic of heterozygote	References
1. Agammaglobulinemia	Gamma globulin levels in blood normal	Gitlin & Janeway (43)
2. Congenital familial nonhemolytic jaundice with kernicterus	Serum bilirubin levels normal	Crigler & Najjar (25)
3. Cystinosis	No evidence of cystinuria or aminoaciduria*	Bickel (14); Robson & Rose (94); Hsia (53).
4. DeToni-Fanconi syndrome	No evidence of renal tubular dysfunction†	Harris (47)
5. Diabetes insipidus (pituitary type)	Normal specific gravity in urine	Canon (20); Forssman (35)
6. Erythropoietic porphyria	No abnormalities in porphyrin metabolism	Kench, Langley & Wilkinson (58); Frankel (36)
7. Fructosuria	Absence of fructose in urine	Lasker (62)
8. H (Hart disease)	No amino-aciduria	Baron, Dent, Harris, Hart & Jepson (8)
9. Methemoglobinemia	No methemoglobin in blood	Gibson & Harrison (40)
10. Pentosuria	No xyloketosuria	Lasker, Enklewitz, & Lasker (61)
11. Thrombocytopenia, eczematoid dermatitis, and bloody diarrhea	No detectable changes	Aldrich, Steinberg & Campbell (4)

* The amino acid disturbances described by Pfändler (86) have not been confirmed. Similarly, there appears to be no basis for believing cystinuria may occur as a heterozygous form of cystinosis (1, 57).

† The three sibs with amino-aciduria, renal glycosuria, mild acidosis, and hypophosphatemia described by Dent and Harris all subsequently developed typical bony changes.

CONDITIONS WHERE THE HETEROZYGOTE HAS NOT BEEN ADEQUATELY STUDIED

Finally, no published data is available on a number of hereditary diseases such as albinism, alcaptonuria, intermittent acute porphyria, etc. In some of these conditions, no specific effort has been made to detect chemical deviations. In others, the total number of cases studied is too small to permit a proper evaluation of the evidence.

DISCUSSION

It would appear that a start has been made toward the detection of "asymptomatic" carriers of mutant genes. Whether this is done by recognizing functional disturbances such as the clotting mechanism, or by the more precise identification of a particular molecule as in sickle cell hemoglobin, their identification can be of considerable value. The use of this knowledge as a direct means of demonstrating the inheritance of a given condition has already been mentioned. When the person possessing a mutant gene can be identified, the possible occurrence of the full-blown disease in the offspring of certain matings can be predicted. The prompt institution of treatment made possible by this foresight may bring about the successful therapy of such conditions as galactosemia and phenylketonuria.

From the present review, it becomes apparent that the concept of dominance and recessiveness can largely be regarded as operational definitions, which for medical and counselling purposes can be quite useful. However, genetically speaking, most conditions are no longer transmitted as a complete dominant or recessive, but relatively so depending upon the ease with which the character can be detected among heterozygotes. Thus, phenylketonuria may be classified as an incompletely recessive condition, sicklemia as being neither dominant nor recessive, but intermediate, and hereditary spherocytosis as an incompletely dominant disease.

It is possible that all carriers of mutant genes would react abnormally if put under sufficient biological stress. The existence of molecules in each carrier, therefore, represents at least a potential medical hazard. The frequency of mutant genes in the population is of considerable medical interest for this reason. Muller (73) has estimated that each individual, on the average, carries eight detrimental mutant genes in heterozygous condition. This represents a more or less familial pattern of weaknesses, most of which are not to be distinguished sharply from disabilities of environmental origin. Under normal conditions, these may only slightly affect an individual's general performance in life, and perhaps increase his susceptibility to non-genetic diseases. In periods of unusual stress, these could well represent the difference between extinction and survival.

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The Genetics of Jewish Populations

I. Finger Print Patterns in Jewish Populations in Israel

LEO SACHS AND MARIASSA BAT-MIRIAM

Department of Experimental Biology, Weizmann Institute of Science, Rehovoth, Israel, and Israeli Institute for Biological Research, Ness Ziona, Israel

INTRODUCTION

THE STATE OF ISRAEL offers unique opportunities for studies in human population genetics. The country contains groups that have lived in some cases for hundreds of years in different parts of the world, and it is an intriguing question both from the point of view of the genetics of human populations in general and from the point of view of the genetic history of the Jews in particular, to determine the similarities and differences between these Jewish communities. Although according to the strict observance of the Jewish religion, Jews should marry only other Jews, it is known that there has been some intermarriage in various parts of the world and the question arises what effect this and the possibility of conversions has had on the gene pool of the Jewish people, and indeed if there is still genetic evidence for such a gene pool.

In order to try to answer these questions we have started a genetic analysis of various Jewish populations. The present paper deals with the results of a study on the finger print patterns of eight Jewish groups in Israel which we have specifically chosen for their historical background. Before presenting the finger print data we will therefore briefly outline the historical background of the groups that we have studied.

HISTORICAL

There have been three main Jewish migrations from this country, since the Jews entered it in about 1200 B.C. (Coon, 1948). The first was caused by the first destruction of the temple and the Babylonian captivity in 586 B.C.; the second was the migration that followed the spread of Greek influence begun by Alexander in 334 B.C.; and the third became particularly marked after the second destruction of the temple by the Romans in 70 A.D. The Babylonian captivity, i.e. the first migration, was officially terminated with the restoration of the country under Cyrus (538 B. C.), but many Jews remained in Babylon and the present Iraqi Jews are presumably to a large extent descendants of this community. The second migration took the Jews to Egypt, Syria, the Balkans, and the Crimea, and the third took the Jews into the Roman world and marked the foundation of settlements in Spain, Germany, Italy and France.

The Jews who originally settled in Germany and Spain spread to other countries and their descendants are known respectively as the Ashkenazim, from the medieval Jewish word for Germany, and the Sepharadim, from the medieval Jewish word for

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Spain. The Ashkenazim spread from Germany to Poland, parts of Russia and other countries in Europe, and they also form the majority of the present day North and South American, English, and South African Jewish communities. The Sepharadim who originally settled in Spain had to leave in 1492 at the time of the Inquisition, and the majority settled in what was then the Turkish Empire. Their descendants can be found in the communities of Turkey and Bulgaria. Others from Spain went to North Africa, where there was already a small group of Jews who claim to have been there since before the Babylonian captivity. There was presumably some intermixing between these populations and as a representative of their descendants we have taken the Jews from Morocco. The Egyptian Jewish community was a flourishing one at the time of Alexander and for some time in the middle ages. The present day Jews from Egypt seem to have a component of these early settlers reinforced to a large extent by the Jews that left Spain at the time of the Inquisition.

In addition to the three main migrations from Palestine, there have been some smaller ones, the descendants of one of which, the Yemenites, have been included in the present investigation. It is supposed that Jews settled in Yemen before the destruction of the first temple and that they continuously lived there since that time. The community today is a very religious one.

The Jewish groups we have studied are therefore those from Yemen; from Iraq, the descendants of the Babylonian emigrants; from Germany and Poland, the descend-

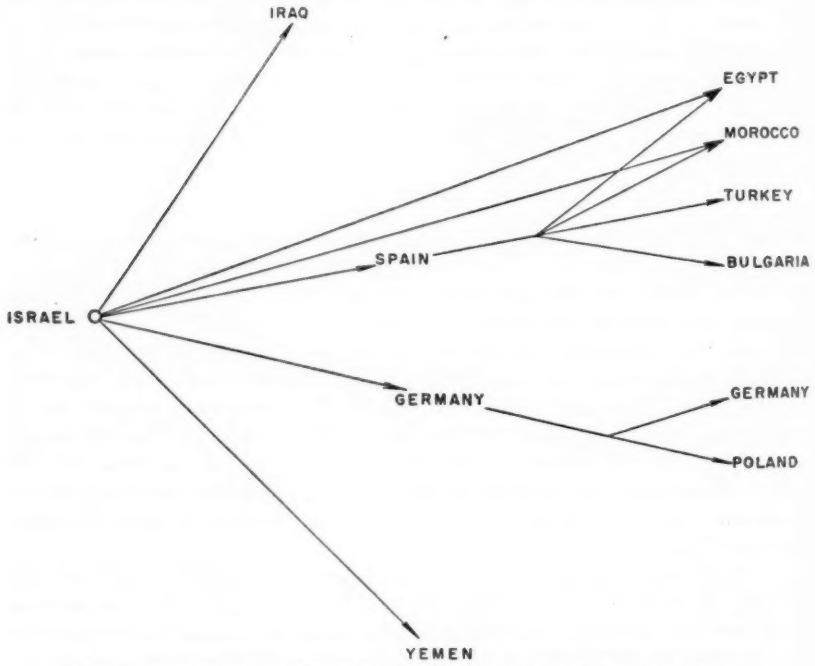

FIG. 1. DIAGRAM OF THE ORIGINAL MIGRATION OF THE JEWISH GROUPS STUDIED

FIG. 2. PHOTOGRAPH (FROM RIGHT TO LEFT) OF A WHORL, LOOP AND ARCH

TABLE 1. THE FREQUENCIES OF WHORLS IN 5 REPLICATE DETERMINATIONS ON 4 JEWISH GROUPS. EACH REPLICATE CONSISTS OF THE DATA FOR 100 PERSONS

Origin	Fingers										Total R	Total L	Total R + L
	R1	R2	R3	R4	R5	L1	L2	L3	L4	L5			
Egypt	52	48	28	58	27	44	48	22	48	22	42.6	36.8	39.7
	58	45	34	60	25	42	37	24	43	22	44.4	33.6	39.0
	61	49	24	72	30	55	50	23	59	27	47.2	42.8	45.0
	54	46	23	59	30	44	40	28	51	18	42.4	36.2	39.3
	54	42	27	59	36	45	39	30	46	20	43.6	36.0	39.8
Mean	*55.8*	*46.0*	*27.2*	*61.6*	*29.6*	*46.0*	*42.8*	*25.4*	*49.4*	*21.8*	*44.0*	*37.1*	*40.6*
S.E. ±	1.6	1.2	1.9	2.6	1.9	2.3	2.6	1.5	2.7	1.6	0.9	1.5	1.1
Germany	63	43	19	62	26	44	31	25	53	18	42.6	34.2	38.4
	53	52	26	60	31	53	33	22	48	25	44.4	36.2	40.3
	67	51	29	69	28	49	47	21	45	21	48.8	36.6	42.7
	52	39	22	55	25	49	43	24	46	16	38.6	35.6	37.1
	56	42	34	57	34	50	45	23	55	24	44.6	39.4	42.0
Mean	*58.2*	*45.4*	*26.0*	*60.6*	*28.8*	*49.0*	*39.8*	*23.0*	*49.4*	*20.8*	*43.8*	*36.4*	*40.1*
S.E. ±	2.9	2.6	2.6	2.4	1.7	1.4	3.3	0.7	2.0	1.7	1.6	0.9	1.1
Turkey	60	49	22	64	25	58	36	25	49	22	44.0	38.0	41.0
	61	38	17	52	17	54	36	22	41	19	37.0	34.4	35.7
	52	38	22	55	20	43	37	22	42	18	37.4	32.4	34.9
	58	51	28	58	23	48	43	33	46	15	43.6	37.0	40.3
	52	41	21	51	17	44	44	21	44	19	36.4	34.4	35.4
Mean	*56.6*	*43.4*	*22.0*	*56.0*	*20.4*	*49.4*	*39.2*	*24.6*	*44.4*	*18.6*	*39.7*	*35.2*	*37.5*
S.E. ±	1.9	2.8	1.8	2.3	1.6	2.9	1.8	2.2	1.4	1.1	1.7	1.0	1.3
Yemen	59	45	30	52	19	52	43	29	44	12	41.0	36.0	38.5
	61	56	29	59	33	48	46	28	50	31	47.6	40.6	44.1
	59	48	33	59	18	50	46	37	49	17	43.4	39.8	41.6
	41	43	21	53	11	53	36	30	50	15	33.8	36.8	35.3
	49	59	32	63	23	39	44	36	58	19	45.2	39.2	42.2
Mean	*53.8*	*50.2*	*29.0*	*57.2*	*20.8*	*48.4*	*43.0*	*32.0*	*50.2*	*18.8*	*42.2*	*38.5*	*40.3*
S.E. ±	3.8	3.1	2.1	2.0	3.6	2.3	1.8	1.9	2.2	3.3	2.4	0.9	1.5

ants of the original Ashkenazim; from Turkey and Bulgaria which to a large extent, and from Morocco and Egypt which probably to a smaller extent, are descendants of the original Sepharadim from Spain (Fig. 1). Representatives of all these groups are now again living in Israel.

RESULTS

The genetic characters we have examined in these eight Jewish populations, and also in an unselected group of Israeli Arabs, are the three basic types of finger print patterns, the whorls, loops and arches (Fig. 2). These characters were chosen because they are presumably as selectively neutral in different environments as any characters that one can hope to find, and previous data (summarized in Cummins and Midlo, 1943, Rife, 1953, and da Cunha and Abreu, 1954) have shown that they can be useful for the determination of ethnic relationships. They show a complex type of inheritance (Cummins and Midlo, 1943, Holt, 1949, and Rife, 1953). For each population we have examined the frequencies of whorls, loops and arches on each of the 10 different fingers in 500 males taken at random. Each group of 500 was analyzed in five replicates of 100 in order to determine the intergroup variations, and men only were chosen in order to avoid any differences due to sex. Particular care was taken to avoid including members of the same family. For each population we have therefore collected data on 5,000 fingers, giving a total of 40,000 fingers for the eight Jewish groups and 5,000 fingers for the group of Israeli Arabs. Owing to their size it can be

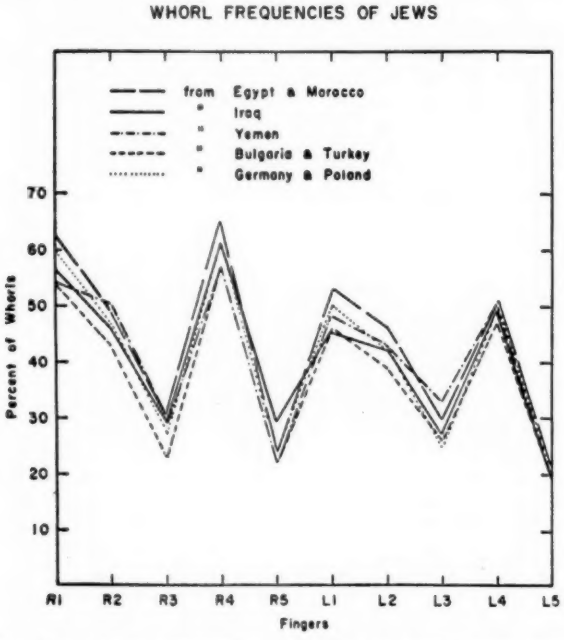

FIG. 3. THE MEAN FREQUENCIES OF WHORLS IN EIGHT JEWISH GROUPS

TABLE 2. THE FREQUENCIES OF LOOPS IN 5 REPLICATE DETERMINATIONS ON 4 JEWISH GROUPS. EACH REPLICATE CONSISTS OF THE DATA FOR 100 PERSONS

Origin	Fingers										Total R	Total L	Total R + L
	R1	R2	R3	R4	R5	L1	L2	L3	L4	L5			
Egypt	48	48	67	41	70	56	43	70	49	78	54.8	59.2	57.0
	42	46	62	39	75	56	57	71	56	78	52.8	63.6	58.2
	36	48	73	28	70	43	47	73	41	73	51.0	55.4	53.2
	46	41	73	41	70	54	51	66	47	81	54.2	59.8	57.0
	46	52	70	40	64	54	51	66	51	80	54.4	60.4	57.4
Mean	*43.6*	*47.0*	*69.0*	*37.8*	*69.8*	*52.6*	*49.8*	*69.2*	*48.8*	*78.0*	*53.4*	*59.7*	*56.6*
S.E. ±	2.1	1.8	2.1	2.5	1.8	2.4	2.3	2.8	2.5	1.4	0.7	1.3	0.9
Germany	37	47	76	38	74	56	61	70	46	81	54.4	62.8	58.6
	45	44	71	40	69	45	57	73	51	75	53.8	60.2	57.0
	33	38	67	30	71	50	47	70	54	79	47.8	60.0	53.9
	43	49	71	44	74	45	44	66	50	83	56.2	57.6	56.9
	42	50	64	42	66	46	48	74	44	76	52.8	57.6	55.2
Mean	*40.0*	*45.6*	*69.8*	*38.8*	*70.8*	*48.4*	*51.4*	*70.6*	*49.0*	*78.8*	*53.0*	*59.6*	*56.3*
S.E. ±	2.2	2.1	2.0	2.4	1.5	2.1	3.2	1.4	2.3	1.5	1.4	0.9	0.8
Turkey	37	37	70	35	74	39	53	66	47	76	50.6	56.2	53.4
	39	55	81	48	83	46	54	75	59	81	61.2	63.0	62.1
	48	53	74	44	80	55	55	67	57	82	59.8	63.2	61.5
	38	40	68	42	77	49	47	60	51	85	53.0	58.4	55.7
	47	52	78	49	83	55	48	72	55	81	61.8	62.2	62.0
Mean	*41.8*	*47.4*	*74.2*	*43.6*	*79.4*	*48.8*	*51.4*	*68.0*	*53.8*	*81.0*	*57.3*	*60.6*	*58.9*
S.E. ±	2.3	3.7	2.4	2.5	1.8	3.0	1.6	2.6	2.2	1.4	2.3	1.4	1.9
Yemen	41	48	69	48	81	48	52	66	56	88	57.4	62.0	59.7
	37	39	69	41	67	51	46	69	47	69	50.6	56.4	53.5
	40	43	66	41	82	50	48	58	51	83	54.4	58.0	56.2
	57	46	78	47	89	45	52	67	50	85	63.4	59.8	61.6
	50	38	65	36	76	59	51	58	41	81	53.0	58.0	55.5
Mean	*45.0*	*42.8*	*69.4*	*42.6*	*79.0*	*50.6*	*49.8*	*63.6*	*49.0*	*81.2*	*55.8*	*58.8*	*57.3*
S.E. ±	3.7	1.9	2.3	2.2	1.8	2.3	1.2	2.3	2.5	3.3	2.2	0.9	1.5

assumed that none of the populations that we have examined are now subject to the genetic drift that may occur in small isolated groups.

The results of five replicate determinations on the frequencies of whorls for each of the 10 fingers in four of the Jewish populations are given in table 1, and the mean values for the eight groups are shown in figure 3. All the Jewish populations, as well as our group of Israeli Arabs, conform to what has been called the "pair group rule" in that there is a greater similarity between fingers 1 and 4 on the same hand than between the same fingers on different hands. This type of conformity is also shown by several other ethnic groups (Rife, 1953).

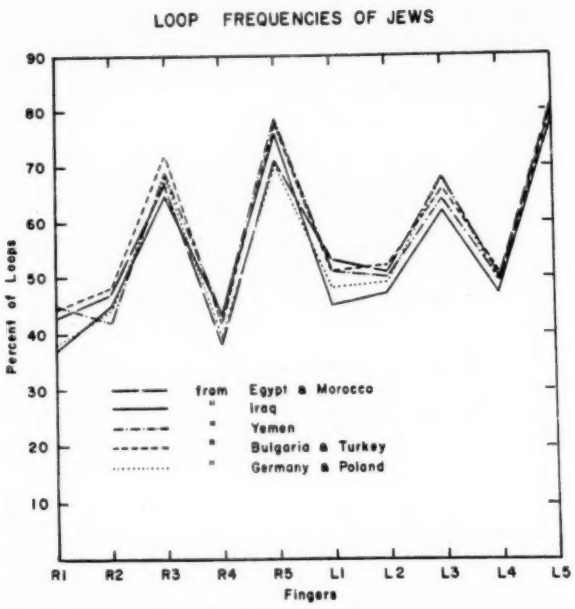

FIG. 4. THE MEAN FREQUENCIES OF LOOPS (RADIAL AND ULNAR) IN EIGHT JEWISH GROUPS

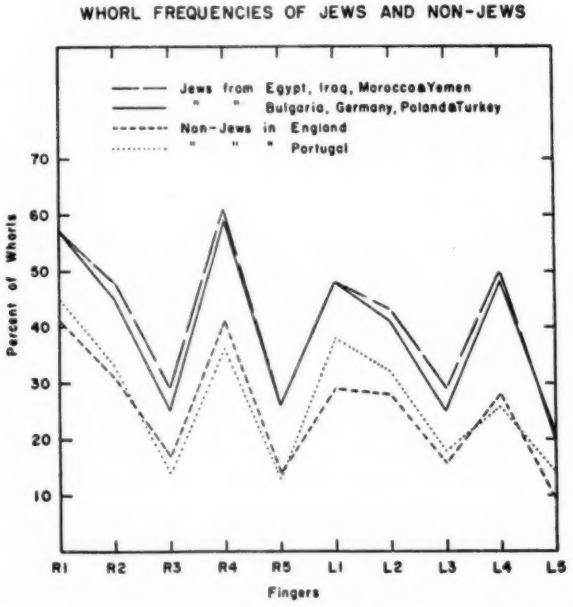

FIG 5. THE MEAN FREQUENCIES OF WHORLS IN EIGHT JEWISH AND TWO NON-JEWISH GROUPS

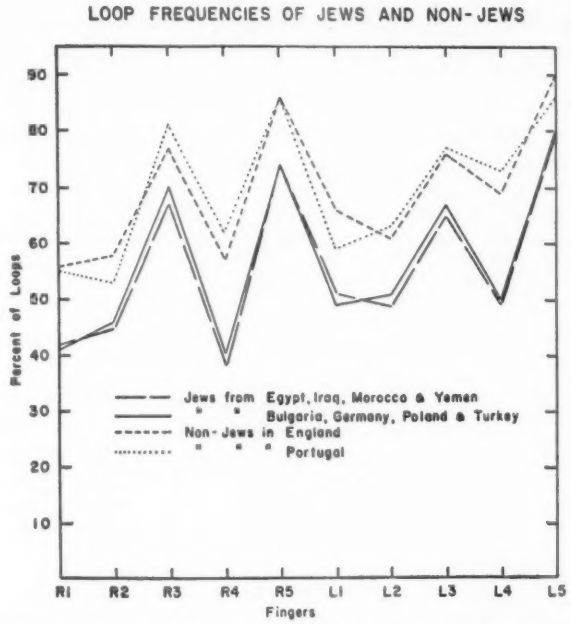

FIG. 6. THE MEAN FREQUENCIES OF LOOPS (RADIAL AND ULNAR) IN EIGHT JEWISH AND TWO NON-JEWISH GROUPS

The present data for the 10 fingers show that there are striking similarities in the frequencies of whorls in the Jewish populations from different countries. These similarities are further confirmed by the frequencies found for loops (table 2, Fig. 4).

As a comparison between our data on Jews and that obtained for individual fingers in some non-Jewish groups, we have shown in figures 5 and 6 the frequencies of whorls and loops in the eight Jewish groups and those found in a sample of 5,000 persons examined in England (Cummins and Midlo, 1943) and a sample of 100 males in Portugal (da Cunha and Abreu, 1954). In both cases the non-Jewish groups differ from all the Jewish ones, and this also applies to a population of non-Jews analyzed in Holland (Dankmeijer, in Rife, 1953) where the frequencies resemble those of the English.

In addition to the data on each of the 10 fingers that can be used for comparison, there is a considerably larger amount of data available in the literature which is given in the form of a pattern index. This index is used to express the total frequencies of whorls, loops and arches in the population, and it is obtained by adding the frequency of loops to twice the frequency of whorls and dividing by 10 if the frequencies are in the form of percentages (Cummins and Midlo, 1943).

The pattern indices for the eight groups of Jews and the one group of unselected Israeli Arabs, arranged in an ascending order, are given in table 3. The combined data for all the Jewish groups give a mean pattern index of 13.67*. It is significant

* Note added in proof: An analysis of 500 Jewish men from Russia has also given a pattern index of 13.62 ± 0.11.

that the index found in the sample of Jews from Germany is 13.65, a figure that is very close to the index of 13.87 found in a sample of 1,037 Jewish men analyzed in Germany (Kirchmair, in Rife, 1953). Two Jewish groups consisting of 144 and 100 men examined in the U.S.A. (Rife, and Cummins and Midlo, in Rife, 1953) have pattern indices of 13.80 and 13.75 respectively, and these figures also fit in well with the results obtained for Jews from other countries.

TABLE 3. THE PATTERN INDICES IN 5 REPLICATE DETERMINATIONS ON 8 JEWISH GROUPS AND 1 GROUP OF ISRAELI ARABS. EACH REPLICATE CONSISTS OF THE DATA FOR 100 PERSONS

Origin	Replicates					Mean	S.E. ±
	1	2	3	4	5		
Bulgaria	13.02	13.02	13.19	13.25	14.04	*13.30*	0.19
Turkey	13.13	13.28	13.35	13.54	13.63	*13.39*	0.09
Germany	13.11	13.54	13.76	13.92	13.93	*13.65*	0.15
Morocco	13.31	13.55	13.63	13.76	14.16	*13.69*	0.14
Egypt	13.56	13.62	13.64	13.70	14.32	*13.77*	0.14
Yemen	13.22	13.67	13.94	13.99	14.17	*13.79*	0.17
Poland	13.23	13.53	13.94	14.11	14.13	*13.79*	0.18
Iraq	13.63	13.72	14.12	14.18	14.25	*13.98*	0.13
Arabs	13.85	13.86	13.89	14.10	14.38	*14.01*	0.10

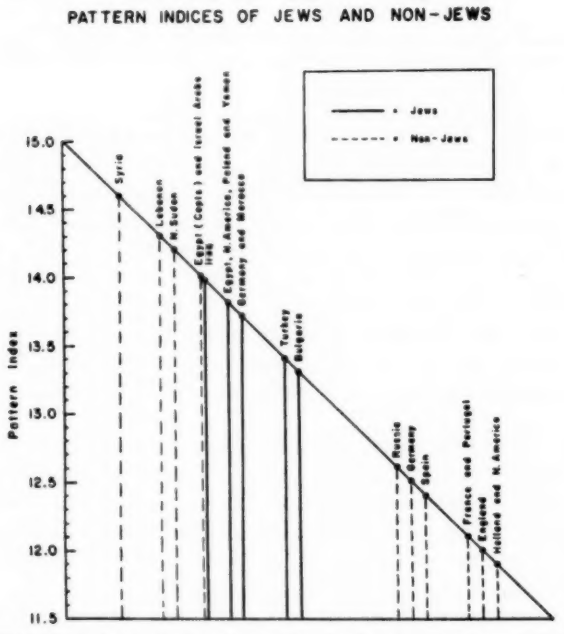

FIG. 7. DIAGRAM OF THE PATTERN INDICES IN VARIOUS JEWISH AND NON-JEWISH GROUPS. THE SPACING ON THE HORIZONTAL AXIS OF THE DIAGRAM HAS BEEN ARBITRARILY MADE SO THAT THE VALUES FOR THE PATTERN INDICES LIE ON A STRAIGHT LINE

The data on pattern indices of Jews and a variety of non-Jewish populations in Europe, N. America and the Middle East, has been compiled in the form of a diagram in figure 7, using for comparison with our data the results of Cummins and Midlo, Dankmeijer, Duis, Leriche, Lopes, Oloriz, Pone, Rife, Shanklin and Cummins, Sannie, Semenovsky, and Waite (Rife, 1943, da Cunha and Abreu, 1954), all of which, like our own, are based as samples of men only. This shows that whereas the non-Jews from Europe and N. America have indices that range from 11.85 to 12.59, none of the Jewish populations, even those that have resided for long periods in these same countries, have such low indices. Similar indices are however found among Jewish groups and some non-Jews from the Eastern Mediterranean region such as the Egyptian Copts and Israeli Arabs.

DISCUSSION

The finger print data have shown that the frequencies of these genetic characters are similar in Jewish populations from different countries. The existence of similar pattern indices among Jews and populations such as Egyptian Copts, which seem to be good representatives of the early Egyptians (Coon, 1948), can be explained in that these similarities are due to their Eastern Mediterranean origin. Even Jews living in Europe and N. America therefore show clear evidence of what one may call their original Eastern Mediterranean gene pool.

Some support for this conclusion can also be seen in the blood group data on the frequencies of Rh subtypes. These show a high frequency of what Mourant has called the typical Mediterranean chromosome, CDe (R_1), in Jews from Europe and Canada (Gurevitch et al, and Chown et al, in Mourant, 1954). It is however desirable that these populations should also be examined for the frequency of D^u which has been found to a considerable extent in at least one Jewish group that has been tested for it (Mourant, 1954). Investigations on physical measurements (Coon, 1948) may also lend support to the conclusions derived from the finger prints.

This analysis of Jews in Israel, and a comparison of the results with other groups, has therefore demonstrated the existence of genetic similarities in a people which has been widely dispersed for centuries in different parts of the world.

SUMMARY

A study has been made on the distribution of finger print patterns in Jews who have come to Israel from Bulgaria, Egypt, Germany, Iraq, Morocco, Poland, Turkey and Yemen. These groups were specifically chosen as representatives of various historical migrations.

Random samples of 500 males in each of these eight Jewish groups have been examined for the frequencies of whorls, loops, and arches, on the 10 fingers. This analysis of 40,000 fingers has shown that these Jewish populations have strong similarities in the frequencies of these genetic characters.

It is further concluded from a comparison of these results with finger print data available in the literature, that there are similar frequencies among Jews and other Eastern Mediterranean populations such as Egyptian Copts, and that even Jewish groups which have resided for long periods of time in Europe (and N. America) show clear evidence of what one may call their original Eastern Mediterranean gene pool.

ACKNOWLEDGEMENT

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Albinism and Sicklemia in a Negro Family*

RALPH W. MASSIE AND ROBERT C. HARTMANN

Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee

ALBINISM IN THE CAUCASIAN presents a well-recognized clinical picture that is unlikely to be overlooked. Although albinism in the Negro is at least as striking and probably more common, it differs in many respects from the picture seen in the caucasian. These differences seem worthy of re-emphasis and are well illustrated in the family to be discussed. The simultaneous occurrence of sicklemia in this family provided an opportunity to study two inherited anomalies in the same family.

The propositus and available family members were carefully examined with reference to the color of the skin, hair, and eyes, and the presence of nystagmus, photophobia, or strabismus. In addition the following blood studies were carried out: complete blood counts, sickle cell preparations, hemoglobin electrophoresis, and fetal hemoglobin determinations.

CASE REPORT OF PROPOSITUS

E. B., (VUH # 247585), a 26 year old single female with negroid features, was referred to the Vanderbilt University Hospital by a vocational rehabilitation service because of extremely poor vision and anemia. The parents were typical Negroes though of moderately light skin pigmentation. Since birth the patient had been "white" and had light yellow hair, pale gray eyes, and "twitching of the eyes." In school she was unable to compete with other children, and apparently because of poor vision only completed the fourth grade. For many years she had had recurrent ankle ulcers recalcitrant to therapy. The patient's family physician discovered anemia about four years prior to her Vanderbilt admission.

The patient was a very tall, thin female with a towering skull, long thin extremities, narrow hips, and arachnoidactily (figure 1). The skin presented a most striking appearance. There was virtually total absence of pigmentation of the skin, nipples, genitalia, and oral, pharyngeal, and nasal mucosa. There were no freckles. The skin over the neck, shoulders, arms, and hands was very thick, coarse, and wrinkled ("elephant skin"). The hair of the scalp and body was very pale yellow (virtually white), and the distribution was typically female.

The irises were very pale gray. The marked lateral nystagmus and extreme photophobia present prevented adequate funduscopic visualization. Vision was impaired and the patient could read only newspaper headlines. Examination of the heart revealed no remarkable findings. The liver and spleen were not palpable. The only other finding of note was the presence of an indolent ulcer 2 cm. in diameter just proximal to the internal malleolus of the left ankle. This particular ulcer had been present for approximately two years.

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FIGURE 1. PROPOSITUS E. B. NOTE THE ABSENCE OF CUTANEOUS PIGMENTATION, THE DRESSING OVER THE ANKLE ULCER, AND THE HABITUS OF SICKLE CELL ANEMIA

The serological test for syphilis and routine urinalysis were negative. Blood counts were: volume of packed red cells 18 per cent, RBC 1.9 million per cmm., hgb. 6.5 grams per cent, reticulocytes 7.1 per cent, WBC 15,700 per cmm., and normal white cell differential count. Hemoglobin electrophoresis revealed a pattern of classical sickle cell anemia (SS). Fetal hemoglobin was 25 per cent.

FAMILY STUDY

Eleven members of the family including the mother, six siblings, one niece, and two nephews were available for the study. The father and one sister of the propositus were deceased. However, this sister's child was available for study. Consanguinity was denied. An additional niece and nephew were unavailable for examination. Statements were obtained from the mother of the propositus regarding skin, hair, and eye color as well as presence of photophobia and nystagmus in her deceased husband, father, mother, three sisters, and one brother. None of these was a definite albino although the mother's brother (uncle of propositus), and mother's parents (maternal grandparents of propositus) were "light-colored" negroes. The former was thought to have light gray eyes as well. In all, reliable information regarding albinism was obtained for four generations, and members of three generations were seen and examined for the presence of albinism and abnormal hemoglobin.

The four examples of albinism were the propositus, two siblings, and one niece. The propositus was the only individual examined who was homozygous for the sickle cell gene (classical sickle cell anemia, SS) although eight of ten remaining individuals were heterozygous (sickle cell trait, SA) for the abnormality. Two were normal (AA). All of the albinos were either homozygous or heterozygous for sicklemia. Only the

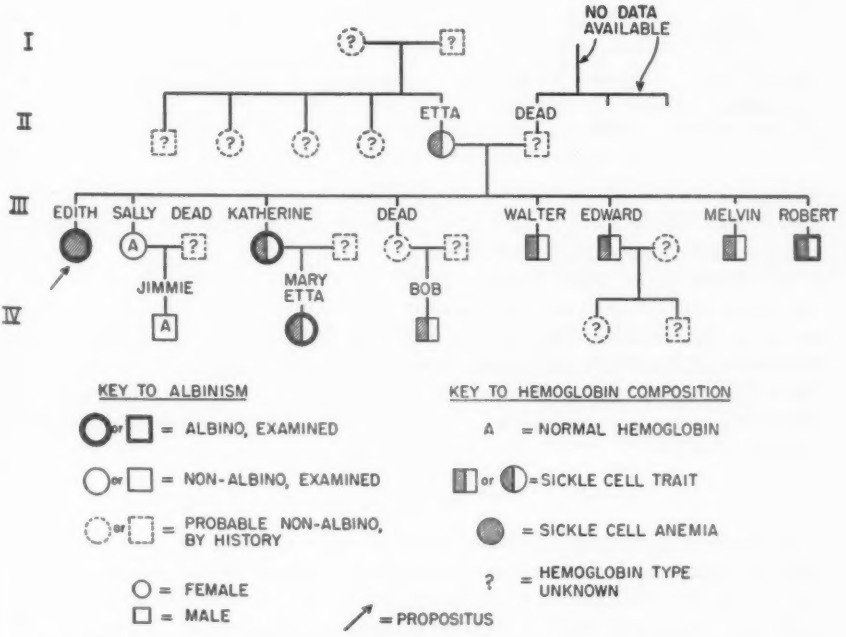

FIGURE 2. FAMILY TREE OF NEGRO FAMILY WITH ALBINISM AND SICKLEMIA. ONLY NAMED MEMBERS OF THE FAMILY WERE EXAMINED

TABLE 1. PHYSICAL CHARACTERISTICS AND LABORATORY STUDIES ON MEMBERS OF FAMILY AVAILABLE FOR EXAMINATION

Name and relationship to propositus	Color of skin	Color of eyes	Nystagmus	Volume of packed red cells—%	Sickle cell preparation	Hemoglobin electrophoretic pattern	Fetal hemoglobin
							%
1. Edith (propositus)	albino	very light gray	present	28	positive	SS	25
2. Etta (mother)	"very light"	gray	absent	43	positive	SA	<2
3. Sally (sister)	"light"	dark brown	absent	42	negative	A	<2
4. Katherine (sister)	albino	very light gray	present + strabismus	42	positive	SA	<2
5. Walter (brother)	"very light"	gray	absent	49	positive	SA	<2
6. Edward (brother)	"light"	dark brown	absent	49	positive	SA	<2
7. Melvin (brother)	"dark"	dark brown	absent	52	positive	SA	2.4
8. Robert (brother)	albino	very light gray	present + strabismus	41	positive	SA	<2
9. Jimmie (nephew) age 8	"dark"	dark brown	absent	42	negative	A	4.7
10. Mary Etta (niece)	albino	very light gray	present	39	positive	SA	<2
11. Bob (nephew)	"dark"	dark brown	absent	39	positive	SA	<2

propositus was anemic and had leg ulcers, body habitus, and other stigmata of sickle cell anemia. Figure 2 presents details of the family tree. Table 1 lists detailed observations on the family members studied.

The father of the albino female in generation IV (Mary Etta) is deceased. While no data is available as to his hemoglobin pattern, the description of his skin, eyes, hair, etc. given by his albino widow and the mother-in-law does not suggest albinism. The possibility of incestuous relationship to account for the albino in generation IV was denied. The albino mother (Katherine), her siblings, and her albino daughter (Mary Etta) are no longer available for further study regarding the occurrence of albinism in generation IV.

DISCUSSION

Albinism is considered to be an inherited disorder involving loss of cutaneous and mucosal pigmentation, ocular abnormalities, and frequent mental retardation (Musser, 1924). The inheritance pattern is thought to be a simple Mendelian recessive with the homozygous state therefore necessary for albinism to be manifest. The incidence has been reported to be 1 in 2900 in Italy, 1 in 9600 in Norway (McCrackin, 1937), and 1 in 144 in southwest Nigeria (Barnicot, 1952). Male and female appear

to be equally affected. Very extensive family data confirming these statements is included in Pearson, Nettleship, & Usher's monograph (Pearson et al, 1913).

In the negro the color of the skin may vary from virtual absence of pigmentation to a light tan color (Barnicot, 1952). Freckling is not uncommon (Musser, 1924; Barnicot, 1952). Thick, coarse wrinkled skin over exposed areas such as the face, neck, hands and arms, is almost universally present (Barnicot, 1952). In the family herein reported all four albinos had almost complete absence of skin pigmentation, and all had the "elephant skin" phenomenon. Freckling and areas of increased pigmentation are thought to be the result of overexposure to sunlight (Barnicot, 1952). This cutaneous change was not observed in our cases.

It has been claimed that there are no negro albinos with pink irises such as occur in caucasian albinos (Barnicot, 1952). In the negro the most common color has been gray, light blue, or rarely brown. All four cases observed in the present family had light gray eyes.

Nystagmus and photophobia are almost universally present (Barnicot, 1952), and were seen in our four cases. Strabismus is frequent in occurrence (Barnicot, 1952), and was present in two of our four albinos. The occurrence of partial albinism or semi-albinism has been postulated (McCrackin, 1937; Loewenthal, 1944). In this situation the skin color has been variously described as "yellow", "red", or "mulatto-like", the hair as reddish-brown or brown, and the irises as pale buff or definitely blue (McCrackin, 1937). The occurrence of nystagmus in partial albinism has been reported by some (Loewenthal, 1944) and denied by others (McCrackin, 1937). "White", "yellow", and "red" negroes appear not only in the same regions in Africa (Loewenthal, 1944) but in the same family (Turner, 1933). It has been stated that semi-albinos are likely to have a high incidence of albinos among their offspring.

The mode of inheritance of the abnormal hemoglobin in sickle cell trait and classical sickle cell anemia has been summarized by Neel (Neel, 1951). The presence of two well understood inherited anomalies in one family provides an excellent opportunity to study linkage. Each of the parents of the individuals of generation III is

TABLE 2. THE GENOTYPES OF THE LIVING OFFSPRING OF THE PARENTS OF GENERATION II AND THE NECESSITY (+) OR LACK OF NECESSITY (−) FOR CROSS-OVERS FOR THEIR DERIVATION, ASSUMING THE MATING IS (1) REPULSION X REPULSION, (2) REPULSION X COUPLING, (3) COUPLING X COUPLING (SEE TEXT FOR FURTHER EXPLANATION)

		Assumed mating		
Genotype of child	Sex	1	2	3
1. SS cc	F	−	+	+, +
2. ss C	F	−	−	+
3. Ss cc	F	+	−	+
4. Ss C	M	−	−	−
5. Ss C	M	−	−	−
6. Ss C	M	−	−	−
7. Ss cc	M	+	−	+

Note: c = gene for albinism
S = gene for sickle hemoglobin

doubly heterozygous. If the genes are linked they may, in each parent (generation II), be in coupling or in repulsion, giving rise to three possible types of mating. As follows:

(1) $\frac{Sc}{sC} \times \frac{Sc}{sC}$

(2) $\frac{Sc}{sC} \times \frac{SC}{sc}$ c = gene for albinism
S = gene for sickle hemoglobin

(3) $\frac{SC}{sc} \times \frac{SC}{sc}$

Table 2 shows the genotypes of each of the surviving offspring and whether or not a cross-over is required for a child's genotype to have been derived from the assumed cross. It is clear that at least one cross-over is required to explain the genotypes of the seven children comprising generation III regardless of the true genotype of the parents. Hence the data exclude absolute linkage. Looser linkage, of course, remains a possibility. Considerably more data will be required to exclude this possibility.

SUMMARY

A negro family with four albinos, one with classical sickle cell anemia and three with sickle cell trait, is reported. The physical characteristics of negro albinos are discussed and contrasted with those seen in the caucasian albino. The present study demonstrates that if the hypothesis of simple Mendelian recessive inheritance in albinism is correct, absolute linkage between the genes for albinism and for sicklemia does not occur, but looser linkage is possible.

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Discordant Heart Anomalies in Twins[1]

IRENE A. UCHIDA AND RICHARD D. ROWE

The Departments of Zoology and Pediatrics, University of Toronto, and The Research Institute of The Hospital for Sick Children, Toronto, Canada

THE ETIOLOGY of the great majority of congenital cardiac malformations remains obscure. Certain environmental factors, such as maternal rubella (Rutstein et al, 1952, Stuckey, 1956) and anoxia (Alzamora et al, 1953), are strongly suspected of having etiological significance in humans.

Support for a genetic hypothesis for congenital heart disease has arisen from an increased incidence of cardiac malformations in certain families (reviewed by Taussig, 1947). In contrast to these reports it has been noted in a number of twins seen at The Hospital for Sick Children in Toronto that only one of each pair had a malformation of the heart. A systematic investigation of all twins referred to the Cardiac Service has therefore been made.

MATERIAL

The present report concerns 26 pairs of twins, 25 of whom were seen at The Hospital for Sick Children and one pair examined outside but referred to Toronto for a diagnosis of zygosity (included by courtesy of Dr. S. M. Burris of Kenora, Ontario, and Dr. Harry Medovy of Winnipeg, Manitoba). Both members of each pair underwent cardiac examinations and tests for the determination of zygosity.

There was no history of any infectious or unusual illness during pregnancy in the mothers of the twins. Detailed family histories were taken but no instance of congenital heart disorder was reported among the relatives nor were there any consanguineous unions.

The original sample included 45 pairs of twins but 19 of these are excluded because of incomplete examination. In eight pairs one or both members of the twins died before sufficient testing was done. One of these was said to be concordant both for a heart defect and for cleft palate. Of the remaining 11 pairs the zygosity is known in six sets (5 DZ, 1 MZ) but there is insufficient evidence regarding the heart of the "normal" twin, while both the zygosity and cardiac status are in doubt in 5 pairs. The difficulties encountered in these 11 pairs are mainly the result of inconveniences involved because the families live in places remote from Toronto.

DIAGNOSIS OF ZYGOSITY

Several tests were carried out to determine the zygosity of the like-sex twin pairs. These included blood groups, digital, palmar and plantar patterns, colour of eyes and hair, shape of ears and general physical appearance.

Among the 26 pairs of twins 13 were found to be monozygotic and 13 dizygotic. Of

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FIGURE 1. MONOZYGOTIC TWINS. SMALLER TWIN HAS VENTRICULAR SEPTAL DEFECT

the 13 monozygotic pairs 11 were identical for at least seven blood group loci (by courtesy of the Rh Laboratory, The Children's Hospital, Winnipeg) including ABO, Rh, MNS, P, Kell, Duffy, Lutheran, Lewis. In the two cases where only a few loci were tested, the dermal configurations and general physical characteristics were so

FIGURE 2. MONOZYGOTIC TWINS (MONOCHORIONIC PLACENTA). SMALLER TWIN HAS TETRALOGY OF FALLOT. (Courtesy of the Children's Hospital, Winnipeg.)

similar as to exclude any doubt that they were monozygotic. There were nine female sets and four male sets. One pair was previously reported (Forsyth and Uchida, 1951), but is included here since the twins were seen by the same services. In all 13 sets the colour of the eyes and hair, as well as the shape of the ears were very much alike. In general appearance 11 pairs were difficult to tell apart. The differences, mainly in size, between the members of the other two sets (Figs. 1 and 2) are presumably the result of the cardiac defect in the smaller twin in each case. In both these cases all the above blood groupings were done.

The type of placenta is known in five of these monozygotic twin pairs: three were monochorionic, one dichorionic with separate circulations and one had two separate placentae. Two of the monochorionic placentae had a common circulation, while the type of circulation in the other is not known.

In the dizygotic group four sets were of like-sex and nine unlike. Serological differences were found in two of the like-sex pairs. In the other two pairs no blood samples were available but in one there was a difference in eye colour and in both the differences in the dermal configurations were so great as to rule out monozygosity with certainty.

TABLE 1. THE ANATOMICAL DEFECT PRESENT IN 26 TWIN MEMBERS AFFECTED BY CONGENITAL HEART DISEASE

	Cardiac Malformation	Monozygotic	Dizygotic	Totals
Cyanotic	Tetralogy of Fallot	2	3	5
	Transposition of great vessels	0	1	1
	Tricuspid atresia	0	1	1
	Aortic atresia	0	1	1
	Dextrocardia with pulmonic stenosis	1	0	1
	Subtotal	3	6	9
Non-cyanotic	Ventricular septal defect	5	2	7
	Auricular septal defect	2	1	3
	Pulmonic stenosis with normal aortic root	2	1	3
	Post-ductal coarctation of the aorta	0	2	2
	Patent ductus arteriosus	0	1	1
	Primary endocardial fibroelastosis	1	0	1
	Subtotal	10	7	17
Total		13	13	26

DIAGNOSIS OF CARDIAC MALFORMATION

The principal point to be established from cardiovascular examinations was the unequivocal presence or absence of congenital heart disease in twin members. One of us (R.D.R.) in reviewing the data has been satisfied that congenital heart disease is present in one member of each pair beyond any doubt and absent in the other member beyond all reasonable doubt[2]. The type of cardiac malformation, with one exception, has been established.

a) *The abnormal twin*

In all except one case previously mentioned the abnormal twin was investigated by a paediatric cardiologist at The Hospital for Sick Children. The minimal investigation consisted of history, physical examination, fluoroscopy, and electrocardiography. All cases had striking evidence of congenital heart disease on physical examination and all had a distinctly abnormal electrocardiogram. An accurate clinical diagnosis was possible, but the type of malformation was confirmed by angiocardiography or cardiac catheterization in six, at operation in three, and by autopsy in a further three cases.

The various diagnoses are shown in table 1.

b) *The unaffected twin*

Seventeen such members were examined by a paediatric cardiologist. In three others the twin was pronounced normal by staff paediatricians and in six the family physician, in response to a request for a detailed cardiovascular examination, supplied the pertinent information. As judged by the usual clinical methods alone (i. e. satisfactory physical growth, absence of cyanosis, clubbing or organic heart murmur, normal pulses and blood pressure) the 26 unaffected twins were regarded as having

[2] Details of the cardiovascular examinations of each twin pair are available upon request to the authors.

normal hearts. A chest X-ray was taken of 21 of these; all revealed normal heart size, contour and lung vascularity. In 18 instances a normal twelve lead electrocardiogram was recorded.

DISCUSSION

Without exception the 26 sets of twins here reported were discordant for congenital heart disease. These results are in keeping with a survey of the literature where discordance is more frequently reported than concordance (table 2). Several sources of bias, however, exist in such a tabulation. When one twin has a malformation which is not shared by his monozygotic partner the case is more likely to be published. Furthermore, discordant cases are frequently assumed to be dizygotic without any proof for such an assumption. On the other hand some discordant twins might be missed when only one is hospitalized, while twins with identical anomalies would excite immediate interest. Unbiased data exist principally in those cases in which the cardiac defect in a twin was not primarily responsible for publication. Even here the discordant outnumber the concordant pairs (table 3).

Attempts to compare the results of twin studies with non-twin data have been criticized because of the existence of prenatal environmental factors unique to twins, especially in the case of monozygotic pairs. The majority of such cases share a common fetal circulation which might theoretically become unbalanced, creating a deficiency in one member (Price, 1950). But of the four cases of monozygotic twins in our sample where the type of placental circulation is known, two had separate blood supplies.

If the twinning processes themselves are of etiological significance it is reasonable to expect a larger proportion of twins among a random group of cardiac patients than in the general population. For the three years 1952 to 1954 inclusive, 1,125 new cases of congenital heart disease were seen in The Hospital for Sick Children. Since all these patients passed through the hands of the Cardiac Staff who were aware of the twin study in progress the ascertainment of twins in this group should be almost complete. Among these patients 14 were members of twin pairs, a frequency of one

TABLE 2. FREQUENCY OF CONCORDANT AND DISCORDANT CONGENITAL HEART DISEASE REPORTED IN THE LITERATURE*

Reported Zygosity	Concordant Pairs	Discordant Pairs
Monozygotic	10	23
Dizygotic	1	9
Doubtful Zygosity	2	27
Total	13	59

* Cases of simple dextrocardia with situs inversus viscerum have not been included.

TABLE 3. FREQUENCY OF CONCORDANT AND DISCORDANT CONGENITAL HEART DISEASE AMONG RANDOM TWINS REPORTED IN THE LITERATURE

Reported Zygosity	Concordant Pairs	Discordant Pairs
Monozygotic	3	9
Dizygotic	0	6
Doubtful Zygosity	2	25
Total	5	40

in 80. In congenital heart disease where the concordance rate is not high each member of a pair of twins has an equal chance of being affected. Thus the probability that a pair of twins will be included in this sample should be approximately twice the frequency of twin pairs in the general population. In Canada the frequency of twin births is one in 83. One twin per 80 heart patients therefore appears to be too low a frequency. However the higher neonatal death rate for twins would lower the frequency of twins in the general population who survive into childhood. This fact along with the possibility that some twins in the cardiac sample may have been missed may well account for the difference between the observed and expected frequencies. In the sample selected for the present study one half instead of the expected one third are monozygotic twins. This discrepancy, though not significantly greater than expected, may be due in part to the greater interest and co-operation shown by the parents and physicians of monozygotic twins.

Crowding in utero can be eliminated as a cause, since the heart is formed during the first trimester of pregnancy. Infection in utero also seems to have been ruled out in the present study.

Discordance among monozygotic twins tends to discount genetic factors in the etiology of a trait. The results of this twin study, therefore, indicate that although in certain families congenital heart disease may be genetic in origin the majority of cases are caused by some uterine factor or factors as yet unknown.

SUMMARY

Twenty-six pairs of twins were examined in detail for zygosity and for congenital heart disease. By tests based on serology, dermatoglyphics and physical characteristics, as well as the examination of the placentae in some cases, 13 pairs were found to be monozygotic and 13 pairs dizygotic. The cardiological studies included a detailed history and physical examination, fluoroscopy, electrocardiography, and in six cases cardiac catheterization and angiocardiography. In six patients the malformation was corrected by surgery or confirmed at autopsy. In every case there was discordance for the cardiac defect. These findings do not support the theory of genetic transmission as reported in some studies of family groups.

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The authors are indebted to Dr. John D. Keith, Dr. Norma Ford Walker and Prof. D. B. W. Reid for their assistance and advice in this study. Their appreciation is also extended to the many physicians who helped in the collection of the material, to the staff of the Cardiac Service and the Rh Laboratories of The Hospital for Sick Children and of the Winnipeg Children's Hospital for their help in the blood analyses.

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BOOK REVIEWS

Biochemical Individuality

By ROGER J. WILLIAMS, New York: John Wiley and Sons., 1956. 214 + xiii pages. $5.75.

ONE OF the bases of the thinking in this book is genetic, but relatively few data on genetics will be found here. What Dr. Williams is mainly concerned with is to emphasize the normal variability of the human body, and the undeniable fact that modern medicine, with its sharp antithesis between the normal and the abnormal, has largely ignored this variability. He points out the obvious but neglected fact that if we take, as is customary, the 95 per cent level as the line of demarkation between normal and abnormal, only 60 per cent (0.95^{10}) would be normal for all of ten characters, and only 0.59 per cent (0.95^{100}) normal for all of 100 characters. I have seen only one other equally clear statement of this simple principle, and this in an article I am sure Dr. Williams never saw, in a science fiction magazine.[1]

Aside from this, the chief original contributions in the present essay are two principles: the *principle of genetic gradients*, which can be phrased as follows: whenever an extreme variation of a genetically controlled character is found in an individual, we should assume (lacking proof to the contrary) that intermediate degrees of this character will be found in other individuals, and the *genetotrophic principle:* Every individual that has a distinctive genetic background has distinctive nutritional needs which must be met for optimal well-being. One consequence of this principle is that different individuals can support different degrees of deprivation of "essential" nutrients before they show signs of impaired health. Williams believes that even alcoholism is in certain individuals a nutritional deficiency disease.

In spite of the title of the book, the author by no means restricts his attention to biochemical variation, except in the sense that anatomical differences are doubtless but the visible sign of biochemical variations. This will be apparent from a list of the chapter headings; Biochemical variation, its significance in biology and medicine; Genetic basis of biochemical individuality; anatomical variations—significance; Individuality in composition; Individual excretion patterns; Endocrine activities; Excretion patterns; Pharmacological manifestations; Miscellaneous evidences of individuality; Individuality in nutrition; The genetotrophic approach; Implications for the biological sciences; Implications for medical and dental research; Implications for advance in psychiatry.

It will be apparent from these titles that the author has managed to cram an amazing amount of data on human individuality into his 214 pages. No further summary of these data can be attempted here.

Since the subject of blood groups is already covered by a large literature, Dr. Williams understandably makes no attempt to do more than mention this subject.

No book is without imperfections; this is no exception. On p. 59 a statement is made which might give the uninformed reader the impression that the secretor phenomenon is confined to individuals of blood group A. On p. 116 the word allergy is used to mean any unusual reaction to a chemical agent, admittedly a loose usage. It is to be feared that the inventor of the term, von Pirquet, followed perhaps by a good many contemporary allergists, would have considered this a very loose use of a term which has already had a checkered career.

[1] "The abnormability of being normal", by Isaac Asimov, Astounding Science Fiction, May 1956.

Although it is not perhaps an imperfection, I cannot refrain from mentioning one other point. Creatine is described as bitter by *Beilstein*, but Williams states that over twenty years ago he found it to be tasteless to many. I have never been able to find anybody who can taste it as bitter.

These are minor points. This fine book will undoubtedly serve as a valuable source of information on human variability for a long time to come. It is well printed on good paper, and has an index.

WILLIAM C. BOYD
Boston University

Heredity and Your Life

By A. M. WINCHESTER, New York: Vantage Press, 1956, pp. 333, $5.00.

WINCHESTER has given us something of a departure in a book on the "facts of life." The first few chapters are more or less standard in their introduction to and discussion of sex and reproduction. In fact, the discussion may be good enough to be objectionable to some persons. However, the remainder of the book departs from tradition in that it centers around a sketchy introduction to genetics and a discussion of popular misconceptions and scientific facts in the relationship between genetics and life.

The mode of presentation is largely as a series of anecdotes with inadequate generalization following each anecdote. To this shortcoming has been added a tendency toward overpopularization. The discussion of unimportant incidents and the refutation of ideas that may not be seriously held by anyone consume many pages. The overpopularization has also produced a variety of quaint titles, so that the chapter on the male is entitled "The Male Carrier," while the section on menstruation is called "The Weeping of a Frustrated Womb."

The standard of writing is quite good and there are few misspellings or typographical errors. Errors of both fact and theory are more common, though they may not exceed a permissible dose. Several of the illustrations are particularly unilluminating and three of the text figures do not show the information that the text indicates will be found there.

Although it may be hoped that they can do better, the adolescents or newlyweds who read *Heredity and Your Life* will not be greatly misled. There may also be a place for this book in college courses on "Life" if the average student does not have a background in genetics.

H. M. SLATIS
Argonne National Laboratory
Lemont, Illinois

LETTERS TO THE EDITOR

To The Editor January 2, 1957

Dear Sir:

The simplified maximum likelihood methods for estimating gene frequencies proposed by me (Boyd, W. C. 1954, Maximum likelihood method for estimation of gene frequencies from MNS data. *Am. J. Human Genet.* 6: 1–10; Boyd, W. C. 1954, Shortened maximum likelihood estimation of Rh gene frequencies. *Am. J. Human Genet.* 6: 303–318; Boyd, W. C. 1954, Letter to the editor. *Am. J. Human Genet.* 7: 444–445) depend upon the fact that in some cases the likelihood equation can be factored into two portions, one of which contains only parameters which are easily and efficiently estimated by elementary methods, leaving in the other portion fewer unknowns to be determined by the usual process of successive approximations. In the case of MNS data resulting from tests with four sera, anti-M, -N, -S, and -s, and in the case of Rh data obtained by testing with anti-C, -c, -D, -E, and -e, it is possible to factor the likelihood equation in two different ways. For instance, in the case of MNS data, if we set $m_s = gm$, $m_S = (1 - g)m$, $n_s = dn$, $n_S = (1 - d)n$, where m and n are the estimates of total m and total n gene frequencies derived by simple gene counting, we may factor the likelihood equation into two parts, one containing only m and n, and the other containing only g and d, and it is essentially upon this fact that the method I proposed (for the results of tests made with three sera) depends. However, in the case of data obtained by testing with four sera, we may also set $m_s = h_s$, $n_s = (1 - h)s$, $m_S = kS$, $n_S = (1 - k)S$, where s and S are the total frequencies of S-negative and S-positive genes estimated by gene counting, and factor the likelihood equation into two parts, one containing only S and s and the other containing only h and k. We can then proceed to find the values of h and k which make the second portion of the likelihood expression a maximum.

The questions might arise, which procedure is preferable, and do the two procedures give the same final results? The answers will doubtless seem obvious to mathematicians, but some who like myself do not fall into this class may be interested to know that it makes no difference which procedure is employed, (the amount of work is the same) and that they give the same answer. This has been verified by working out the maximum likelihood gene frequencies by both methods (outlines of these procedures will be sent to readers on request) for the data on 161 pure-blooded Chippewa Indians tested by Matson, Koch and Levine (Matson, G. A., E. A. Koch, and P. Levine 1954, A study of the hereditary blood factors among the Chippewa Indians of Minnesota. *Am. J. Phys. Anthrop.* 12: 413–426; Mourant, A. E. 1954 *The Distribution of the Human Blood Groups*, Springfield, Ill.: Charles C. Thomas, p. 365). Starting with the gene frequencies given by Mourant, both procedures lead to the gene frequencies $m_s = 0.41896$, $m_S = 0.30153$, $n_s = 0.23942$, $n_S = 0.04008$. It will be noted that these frequencies are consistent with the gene counting estimates both of m and n and of S and s.

The maximum likelihood estimates are definitely superior to those given by Mourant, although these too are consistent with both sets of gene counting estimates. The expected frequencies derived from Mourant's frequencies give a value of $\chi^2_{(6)} = 6.586$, whereas the maximum likelihood frequencies lead to a $\chi^2_{(6)}$ of 4.344. The maximum likelihood estimates are also somewhat better than those derived by Levene and Pollitzer (Matson, G. A., E. A. Koch, and P. Levine 1954, A study of the hereditary blood factors among the Chippewa Indians of Minnesota. *Am. J. Phys. Anthrop.* 12: 413–426), for their gene frequencies lead to a $\chi^2_{(6)}$ of 4.752.

However, it must be admitted that the above results could have been predicted in advance, for it has been proved (Cramér, H. 1951, *Mathematical Methods of Statistics*, Princeton, N. J.: Princeton Univ. Press) that if an efficient estimate of a parameter exists, the likelihood equation will have a unique solution equal to this estimate. It would, therefore, be impossible for maximum likelihood methods to give results which did not agree. The results reported here might however, be regarded as proof, for those who have felt misgivings (Mourant, A. E. 1954, *The Distribution of the Human Blood Groups* Springfield, Ill.: Charles C. Thomas), that the simplified methods are maximum likelihood methods with full efficiency.

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WILLIAM C. BOYD
Boston University, School of Medicine
Boston, Massachusetts

To the Editor March 1, 1957
Dear Sir:

A clew leading towards possible explanation of the high frequency of the gene or genes assumed to produce diabetes mellitus may lie in the rapid growth and early sexual maturity which has been reported among diabetics. If it could be demonstrated that patients with post-adolescent onset tend to develop sexually at appreciably earlier ages than (supposed) non-diabetics it would be suggestive of procreative advantage.

With this objective a preliminary survey was made of diabetic girls, 222 with onsets before age 11 and 219 with onsets at 18 or over. The average menarchial ages of these groups were 13.96 and 12.85 years, respectively; the standard deviations 1.89 and 1.275 years. The difference is about seven times its probably error. (Through the kindness of Dr. Priscilla White of the Joslin Clinic, Boston, Massachusetts, the data were obtained from active and former patients).

No comparable group of non-diabetics has been found in the literature with as late an average menarchial age as these childhood onset cases, nor any with as early an average as that of the post-adolescent group. However, comparisons are not statistically justifiable because of the possibility of bias for several reasons: (1) the data were collected from patients by mailed questionnaire while comparative data found in the literature were taken from medical records or physical examination records of University students; (2) approximately one third of the diabetics failed to reply, for reasons unknown—reasons which might lead to bias; (3) patients' ages at the time of questioning ranged from 18 to 40, while the data from comparison groups (of the same year of birth) were collected when the girls were in their late teens.

While more data on the menarchial age of post-adolescent diabetics and controls are needed, taken under conditions conducive to increasing the reliability of results and of diminishing the bias, the average of 12.85 years of one group of 219 is sufficiently low to be suggestive of significant differentiation from non-diabetics.

RICHARD H. POST
Institute for the Study of Human Variation
Columbia University

To the Editor Jan. 30, 1957
Dear Sir:

A sociologist sees special significance in the Report of the National Academy of Sciences—National Research Council on the Biological Effects of Atomic Radiation, because for the first time competent scientists assume responsibility for alerting society to the dangers involved in a new technological process.

Sociologists have long known that the problems of cultural lag which accompany technological advance are difficult of solution, because of inadequate information, the inertia of established thoughtways and institutions, prejudice, and the opposition of vested interests. Where the information needed is of a technical nature, implicit in the device or process causing the social change, the specialists in the technical field have the obligation to furnish all the data their investigations can produce. That obligation is undertaken in this report.

It is to be expected that some, even among the scientists, will object to this new development. Opposition may also be expected from those who see, in the reiterated insistence in the report on the vital necessity of international collaboration in study and control, the beginnings of undesirable political involvements. Some will ridicule and more will ignore the warnings that deleterious muta-

tions threaten the human race if the level of radioactivity is increased. Those representing interests which might be inconvenienced or subjected to loss can be counted upon to protest in the name of science or even patriotism. We will be told that the recommendations imply the assuming of unnecessary expense, the creation of cumbersome systems and the growth of bureaucracy.

It is clear that action on the report involves issues in the field of public opinion and that if the direction indicated by this report is followed, (as it is in the report of December 31, 1956 to the A.A.A.S., on the Impact of Science on Social Forces) there will be objections that scientists are in danger of losing their objectivity and of being drawn into politics and propaganda.

Political action is probably the chief means in a democracy of achieving wide-spread social control. Such control should rise from the assent of the people, hence, popular education through the systematic presentation of essential facts in terms that ordinary people can understand is necessary. This might be called propaganda, but it implies no disloyalty to the scientific method.

Finally, the sociologist is especially interested in the implications of the report with respect to the quantity and quality of the world's human population. While irradiation of foods and the use of radio-isotopes as tracer elements may improve the quality and preserve the values of food, we are told that no great increases in quantity are to be expected. Sociologists, however, look with some misgivings on the rapid increase in world population; increases that are likely to be accelerated in the non-Western areas as medical knowledge and public health measures become widely disseminated, reducing the death rate sharply while the birth rate remains high. It is anticipated that to feed this increased population the oceans will be drawn upon much more heavily for food, but at least three committees stressed that radio-active contamination caused by fall-out from weapons' tests, improper disposal of waste products of fission processes, and accidental discharges is carried around the world by air currents, falls to earth, enters the soil, and eventually the seas. If the radio-active contamination increases to the point where it enters the food chains of the oceans, in the long run, the vastly increased numbers of people every where on earth, making greater and greater use of ocean food supplies, will ingest dangerous doses of radio-active elements. Over the long series of generations genetic deterioration of the whole human race is possible.

In short, the sociologist sees in this report a series of warnings that mankind must act now through old and new social structures and processes to achieve international collaboration in study and control to the end that the human race may avoid irreparable biological damage and that the untold benefits of nuclear energy may be enjoyed.

HENRY M. BUSCH,
Professor of Sociology,
Western Reserve University